# ENDOCRINE AND METABOLIC SEQUELAE OF TUMOURS WITH A FOCUS ON CRANIOPHARYNGIOMA

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# ENDOCRINE AND METABOLIC SEQUELAE OF TUMOURS WITH A FOCUS ON CRANIOPHARYNGIOMA

Endocriene en metabole gevolgen van tumoren
met een focus op craniopharyngiomen

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# Chapter 1

**General introduction and aims and outline of this thesis**

## CANCER, CANCER SURVIVAL, AND LONG-TERM CONSEQUENCES OF CANCER SURVIVAL

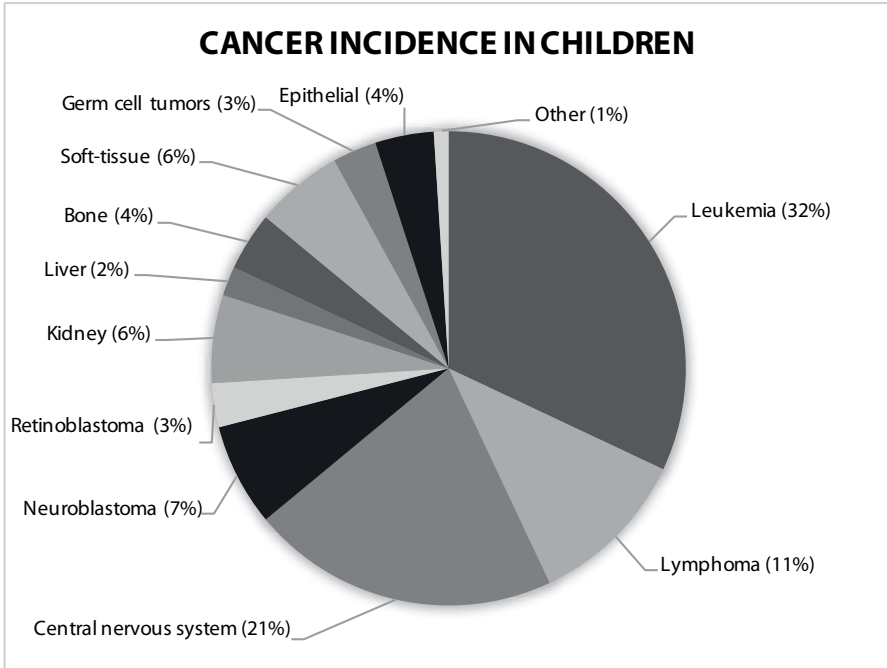### Cancer: an important public health concern

Cancer is one of the most important public health concerns of today. In 2012, worldwide, approximately 14.1 million individuals were diagnosed with cancer, and approximately 32.6 million people lived with cancer.[1] Cancer affects both children and adults. Approximately 1% of all cancers occur in children.[2] Leukaemia, brain cancer, and lymphoma are the most common malignancies in children.[3] Adults predominantly present with lung cancer, breast cancer, and colorectal cancer (Figure 1.1).[4] In children, solid tumours are typically derived from embryonal tissues (i.e. blastomas); adults predominantly manifest solid tumours from epithelial tissues (i.e. carcinomas).[5] Cancer development depends on several factors, including host factors (e.g. genetics, epigenetics, aging), lifestyle factors (e.g. tobacco use, alcohol consumption, unhealthy diet, physical inactivity), environmental factors (e.g. asbestos, pesticides, air pollution), and infectious agents (e.g. *Helicobacter pylori*, Epstein-Barr virus, human papillomavirus, hepatitis B and C).[6] In 2012, approximately 8.2 million individuals died from cancer worldwide.[1] Globally, cancer is the fifth leading cause of death in children and the second leading cause of death in adults.[7]

### Cancer survival and long-term consequences of cancer survival

During the past decades, cancer mortality has declined substantially in both children and adults (Figure 1.2).[8] This is due to several factors, including primary and secondary prevention efforts (e.g. tobacco discouragement policies, cancer screening practices), as well as improvements in cancer treatment and care (e.g. multi-agent chemotherapy, combined-modality treatment, enhanced treatment stratification, advances in supportive care).[9-12] The decrease in cancer mortality is accompanied by an increase in long-term cancer survival.[13-16] To date, in Europe, approximately 78% of children and 58% of adults survive at least five years after cancer diagnosis.[14, 15] Accordingly, awareness of and insight in long-term health effects of cancer and its treatment have become increasingly important.[17-22] Most knowledge on long-term complications of cancer and its treatment has been gained from studies in survivors of childhood, adolescent, and young adult cancer. Reports on late effects in older adults with cancer are limited.

Studies on the health status of survivors of childhood cancer report a high prevalence of chronic health conditions. At an attained age of 45 years, approximately 95% of childhood cancer survivors suffer from at least one chronic health condition; in approximately 80%, this concerns a serious/disabling or life-threatening condition.[23] Chronic health conditions are significantly more common in childhood cancer survivors compared to control subjects not treated for cancer. A recent report from the Childhood Cancer

**Figure 1.1.** Global cancer incidence

## CANCER INCIDENCE IN CHILDREN

Germ cell tumors (3%)
Epithelial (4%)
Other (1%)
Soft-tissue (6%)
Leukemia (32%)
Bone (4%)
Liver (2%)
Kidney (6%)
Retinoblastoma (3%)
Neuroblastoma (7%)
Lymphoma (11%)
Central nervous system (21%)

**A:** Children (i.e. <15 years of age). Data from Steliarova-Foucher et al.[3]

## CANCER INCIDENCE IN ADULTS

Stomach (7%)
Breast (12%)
Prostate (8%)
Central nervous system (2%)
Cervix and uterus (6%)
Colorectal (10%)
Other (28%)
Leukemia (2%)
Liver (6%)
Esophagus (3%)
Lymphoma (3%)
Lung (13%)
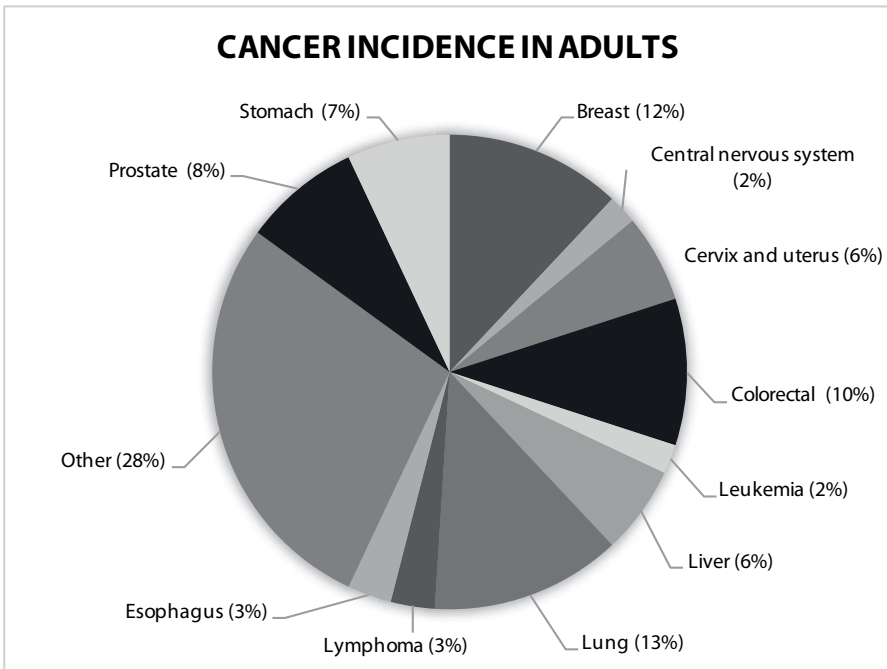
**B:** Adults (i.e. ≥15 years of age). Data from Ferlay et al.[4]

**Figure 1.2.** Cancer mortality in the Netherlands (1950-2013)



**Cancer mortality in the Netherlands (1950-2013)**
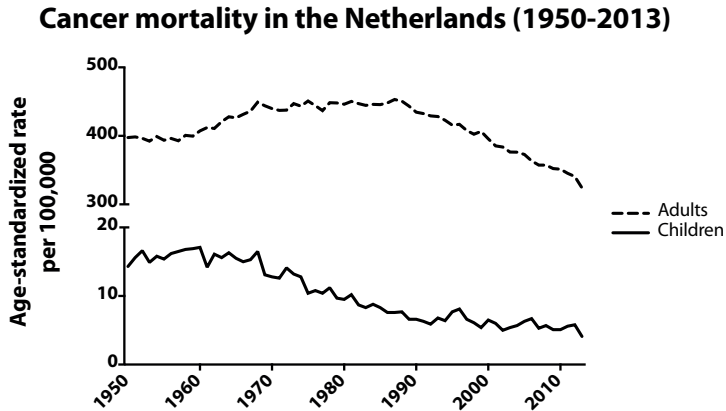
Solid line represents children (i.e. <15 years of age). Dashed line represents adults (i.e. ≥15 years of age). Data from the World Health Organization.[8]
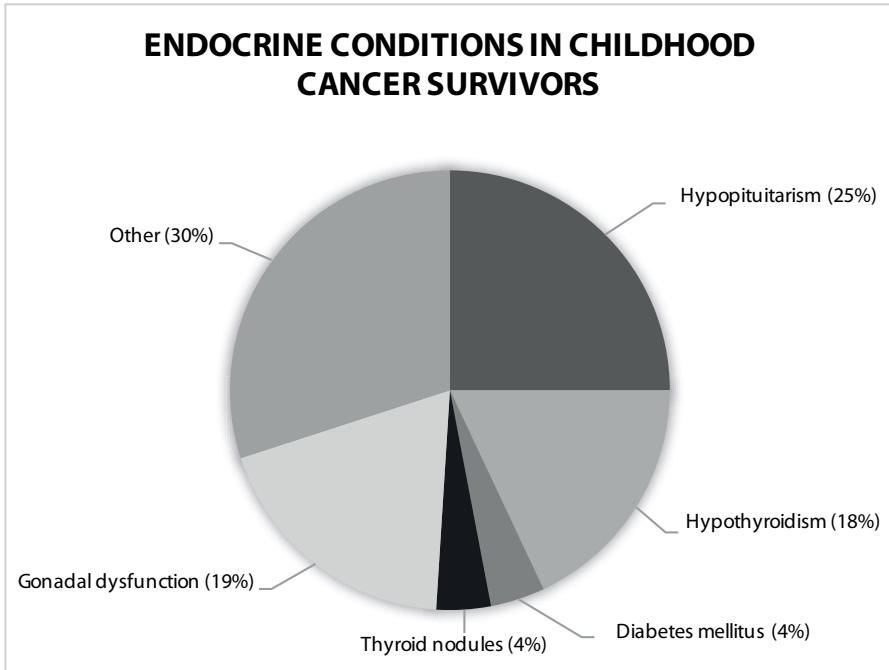
Survivor Study found survivors of childhood cancer to be four times more likely to be diagnosed with a severe, disabling, life-threatening, or fatal health condition compared to their siblings.[24] Studies in survivors of adult cancer report a health status more or less similar to control subjects not treated for cancer.[25-27] This seems to be due to a coincident high prevalence of chronic health conditions in elderly individuals not treated for cancer, as well as to a survivorship bias in cancer survivors participating in the available studies. Smith et al. reported that at an attained age of 75 years, approximately 85% of adult cancer survivors compared to 84% of non-cancer control subjects suffer from at least one chronic health condition.[28] However, some specific chronic health conditions, like cardiovascular disease, type 2 diabetes mellitus, and osteoporosis occur significantly more often in survivors of adult cancer compared to elderly individuals not treated for cancer.[28-31]

Both survivors of childhood and adult cancer are at increased risk for premature mortality.[32-38] In childhood cancer survivors, excessive mortality is mainly due to secondary malignancies, as well as circulatory and respiratory diseases.[32, 33] Adult cancer survivors mainly die from secondary malignancies, digestive diseases, and suicide.[34-38]

**Long-term endocrine and metabolic consequences of cancer and its treatment**

Endocrine and metabolic conditions are among the most frequent long-term sequelae of both childhood and adult cancer (Figure 1.3). At an attained age of 35 years, approximately 60% of childhood cancer survivors are diagnosed with an endocrine condition.[23] In adult cancer survivors, nearly 85% suffers from an endocrine morbidity by the age of 60 years.[31] Hypopituitarism, gonadal dysfunction, and hypothyroidism have been reported to be the most frequent endocrinopathies in childhood cancer survivors;[39] adult cancer sur-

**Figure 1.3.** Endocrine conditions in cancer survivors



**ENDOCRINE CONDITIONS IN CHILDHOOD CANCER SURVIVORS**

Hypopituitarism (25%)

Other (30%)

Hypothyroidism (18%)

Gonadal dysfunction (19%)

Thyroid nodules (4%)

Diabetes mellitus (4%)

**A:** Childhood cancer survivors (i.e. <21 years of age). Data from de Fine Licht et al.[39]



**ENDOCRINE CONDITIONS IN ADULT CANCER SURVIVORS**

Other (7%)

Hypothyroidism (12%)

Gonadal dysfunction (30%)

Thyroid nodules (16%)

Diabetes mellitus (21%)

Osteoporosis (14%)
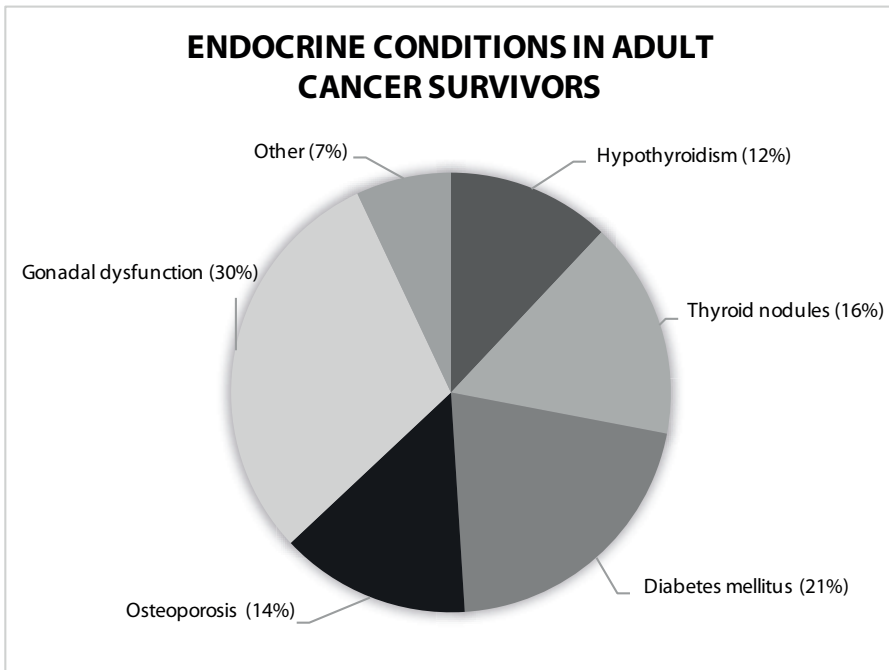
**B:** Adult cancer survivors (i.e. ≥21 years of age). Data from Gebauer et al.[31]

vivors predominantly present gonadal dysfunction, type 2 diabetes mellitus, and thyroid nodules.[31] In childhood cancer survivors, the highest risks for endocrine disorders have been reported in patients treated for brain cancer, leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and neuroblastoma.[39] In adult cancer survivors, most studies focused on patients treated for breast cancer, prostate cancer, testicular cancer, lymphoma, and brain cancer.[40] The increased risk for endocrine conditions in cancer survivors is related to administered treatment modalities, like radiotherapy and chemotherapy (Table 1.1).[41, 42]

Among the most important long-term health effects in cancer survivors are subsequent neoplasms. After 30 years of follow-up since primary cancer diagnosis, approximately 21% of childhood cancer survivors and 19% of adult cancer survivors are diagnosed with a second tumour.[43] Endocrine-related cancers, including tumours of the breast and thyroid, are among the most frequent secondary neoplasms.[16, 44]

Many endocrine conditions adversely affect metabolism. Accordingly, several studies investigated metabolic risk factors in cancer survivors.[45, 46] In both childhood and adult cancer survivors an increased incidence of obesity, insulin resistance, dyslipidaemia, and elevated blood pressure has been reported.[47-50] The clustering of these related risk factors is referred to as the metabolic syndrome.[51] The metabolic syndrome has been reported in 6-39% and 8-49% of childhood and adult cancer survivors, respectively.[48-50] The metabolic syndrome has been associated with a two-fold increased risk for cardio- and cerebrovascular disease, as well as a five-fold increased risk for type 2 diabetes mellitus.[52] An unhealthy lifestyle with insufficient physical activity has been proposed as an important risk factor for the metabolic syndrome.[53, 54] To date, several reports evaluated physical activity in cancer survivors.[55, 56] However, most were limited by the use of a non-validated questionnaire that did not assess daily life physical activity. In addition, many lacked comparison to a non-cancer control group.

With more than 32.5 million long-term cancer survivors worldwide,[57] the study and follow-up care of this patient population is crucial. Most studies that investigated long-term consequences of cancer and its treatment focused on individuals with a malignant tumour. However, some benign neoplasms may also cause substantial long-term health effects. This is not only because of a destructive tumour behaviour, but also due to a critical localization and need for local aggressive therapy. An important example is craniopharyngioma.

## CRANIOPHARYNGIOMA

### Background and epidemiology

Craniopharyngiomas are benign intracranial tumours that often contain calcifications and fluid-filled cysts. From a treatment perspective, their locally aggressive behaviour

**Table 1.1.** Treatment-related risk factors for endocrine and metabolic disorders in cancer survivors

| Organ system | Morbidity | Treatment-related risk factors |
|---|---|---|
| Hypothalamic-pituitary | Hypopituitarism (GH, FSH/LH, ACTH, TSH, ADH deficiency) | Cranial radiotherapy<br>Total body irradiation<br>Neurosurgery |
| | Hyperprolactinemia | Cranial radiotherapy |
| | Growth failure | Antimetabolites<br>Glucocorticoids<br>Cranial radiotherapy |
| | Precocious puberty | Cranial radiotherapy |
| | Delayed puberty | Cranial radiotherapy<br>Pelvic radiotherapy<br>Glucocorticoids |
| Thyroid | Primary hypothyroidism | Neck, mantle, spine radiotherapy<br>Total body irradiation |
| | Primary hyperthyroidism | Neck, mantle, spine radiotherapy |
| | Thyroid nodules and secondary neoplasms | Neck, mantle, spine radiotherapy<br>Anthracyclines |
| Breast | Secondary neoplasms | Neck, mantle, chest, abdominal radiotherapy<br>Total body irradiation<br>Anthracyclines |
| Gonad | Acute ovarian failure and premature ovarian insufficiency | Alkylating agents<br>Pelvic radiotherapy<br>Total body irradiation<br>Oestrogen deprivation |
| | Leydig and germ cell dysfunction | Alkylating agents<br>Pelvic radiotherapy<br>Total body irradiation<br>Androgen deprivation therapy |
| Bone | Osteoporosis | Glucocorticoids<br>Antimetabolites<br>Aromatase inhibitors<br>Tamoxifen (premenopausal women only)<br>Androgen deprivation therapy |
| Metabolism | Obesity | Cranial radiotherapy<br>Glucocorticoids<br>Oestrogen deprivation<br>Androgen deprivation therapy |
| | Metabolic syndrome and type 2 diabetes mellitus | Cranial radiotherapy<br>Abdominal radiotherapy<br>Total body irradiation<br>Glucocorticoids<br>Oestrogen deprivation<br>Androgen deprivation therapy |

ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; FSH/LH = follicle stimulating hormone/luteinizing hormone; GH = growth hormone; TSH = thyroid stimulating hormone. Data from Rose et al.[41] and Shahrokni et al.[42]

and proximity to critical neurovascular structures (e.g. hypothalamus, pituitary, optic nerves, carotid arteries) make them challenging tumours (Figure 1.4A).[58] Craniopharyngiomas were already described in 1857 by Von Zenker.[59] In 1904, Erdheim was the first to describe their histopathological features.[60] Halstead performed the first craniopharyngioma resection in 1909.[61] Of note, this was a transsphenoidal resection. In 1910, the first transcranial resection was performed by Lewis.[62] At that time, different terminologies were used to describe these tumours. In 1931, Frazier named them craniopharyngiomas,[63] which was further popularized by Cushing in 1932.[64]

Craniopharyngiomas are rare with an estimated incidence rate of 1.34 per million person-years. They affect children and adults, and present with peak incidences between 5-9 and 40-44 years of age.[65] Craniopharyngiomas account for 3% of all intracranial tumours in children and 0.6% of all intracranial neoplasms adults.[66] Approximately 30% of all craniopharyngiomas present in children.[67]

### Location, pathology, and pathogenesis

Craniopharyngiomas arise from remnants of the craniopharyngeal duct, which is an embryonic structure formed during pituitary development (Figure 1.4B).[68] Most craniopharyngiomas have a suprasellar origin with an intrasellar extension (75%); some remain suprasellar (20%). Entirely intrasellar craniopharyngiomas are less common (5%).[69] There are two histological subtypes of craniopharyngioma (i.e. adamantinomatous and papillary) (Figure 1.5). The adamantinomatous subtype contains calcifications and cysts filled with a cholesterol-rich machinery oil-like fluid. The papillary subtype is solid or unicystic without calcifications.[70] Approximately all craniopharyngiomas in children are adamantinomatous. In adults, papillary craniopharyngiomas are more frequent (65%).[71]

The pathogenesis of craniopharyngiomas remains poorly understood. There are two theories on their development. The first is the embryogenetic theory, which suggests that craniopharyngiomas arise from mutated cell rests of the (in those cases) not entirely involuted craniopharyngeal duct.[72] The second is the metaplastic theory, which implies that craniopharyngiomas develop from metaplastic cells of the anterior pituitary.[73] Over the past years, significant progress has been made in understanding the genetic mechanisms underlying craniopharyngioma development. In the adamantinomatous subtype, activating somatic mutations in *CTNNB1* have been found, which result in β-catenin-accumulating cell clusters with over-activation of the Wnt/β-catenin pathway.[74] Recently, Andoniadou et al. demonstrated that these cell clusters promote craniopharyngioma tumorigenesis by autocrine and paracrine mechanisms.[75] In the papillary subtype, *BRAF* p.V600E mutations have been reported.[76] Four families with multiple craniopharyngioma cases have been reported.[77-80] However, an underlying genetic predisposition has never been verified.

**Figure 1.4.** Neuroanatomy and pituitary development
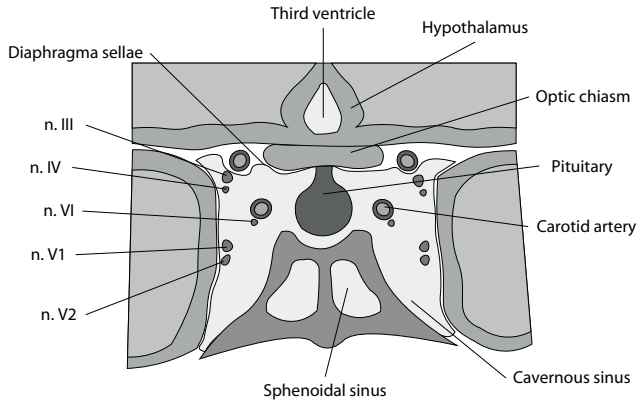


**A:** Anatomy of the (para)sellar area. n. III = oculomotor nerve; n. IV = trochlear nerve; n. V1 = ophthalmic nerve; n. V2 = maxillary nerve; n. VI = abducens nerve.
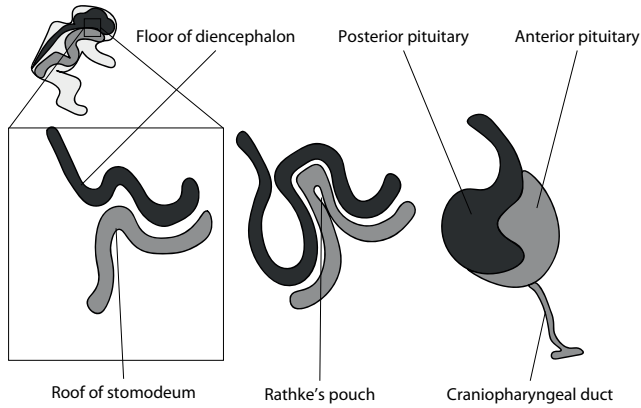


**B:** Pituitary development.
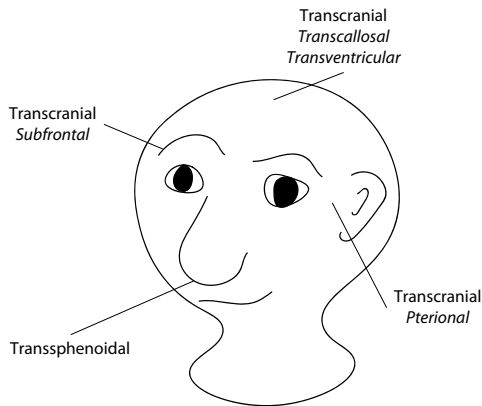


**C:** Neurosurgical approaches.

## Presenting symptoms and imaging modalities

In children, craniopharyngiomas often present with growth failure, headaches, and visual impairment. In adults, the most common presenting features are hypogonadotropic hypogonadism, growth hormone deficiency, and visual field defects (Table 1.2).[81-83] In both children and adults, the duration from symptom onset to craniopharyngioma diagnosis has been reported to be approximately 12 months.[81] However, Müller et al. observed that most children with craniopharyngioma already show a reduced growth rate 7.5 years before diagnosis. In their study, concomitant weight gain was a late manifestation.[84]

Magnetic resonance imaging with and without gadolinium contrast enhancement and unenhanced computed tomography are the imaging modalities of choice for the detection and characterization of craniopharyngiomas. Computed tomography is particularly important for visualizing calcifications (Figure 1.6).[85]

**Table 1.2.** Manifestations of craniopharyngiomas

| Presenting features | All patients (%) | Children (%) | Adults (%) |
| --- | --- | --- | --- |
| Headaches | 49-64 | 46-78 | 50-59 |
| Visual acuity disorder | 39-78 | 39-66 | 40-83 |
| Visual field defect | 55-72 | 46 | 60-77 |
| Hydrocephalus | 16-25 | 34-47 | 7-19 |
| Neurological deficits | 3-18 | 4-34 | 2-10 |
| Epilepsy | 2-4 | 2-3 | 3-5 |
| Cognitive impairment | 14-23 | 5-10 | 17-27 |
| Behaviour changes | 8-11 | 5-10 | 8-13 |
| Altered level of consciousness | 3-6 | 3-10 | 3-4 |
| Anorexia or weight loss | 10-12 | 10-20 | 8-10 |
| Obesity or weight gain | 10-15 | 5-8 | 13-17 |
| Growth hormone deficiency | 52-95 | 56-100 | 51-86 |
| Hypogonadotropic hypogonadism | 74-82 | NA | 74-82 |
| Secondary adrenal insufficiency | 34-62 | 40-68 | 33-58 |
| Secondary hypothyroidism | 26-36 | 25-26 | 26-42 |
| Diabetes insipidus | 14-18 | 6-22 | 15-17 |

NA = not accessible. Data from Karavitaki et al.[81], Nielsen et al.[82], and Du et al.[83]

## Craniopharyngioma treatment

Craniopharyngiomas are generally treated with neurosurgical resection, followed by radiotherapy in case of residual or progressive disease. Alternative treatment options include primary cyst drainage, intracystic appliance of β-emitting isotopes (e.g. ⁹⁰Yttrium) or chemotherapeutic substances (i.e. bleomycin or interferon-α), and stereotactic radiosurgery.[86] Neurosurgical resection can be performed either transcranial or trans-

**Figure 1.5.** Histological subtypes of craniopharyngioma
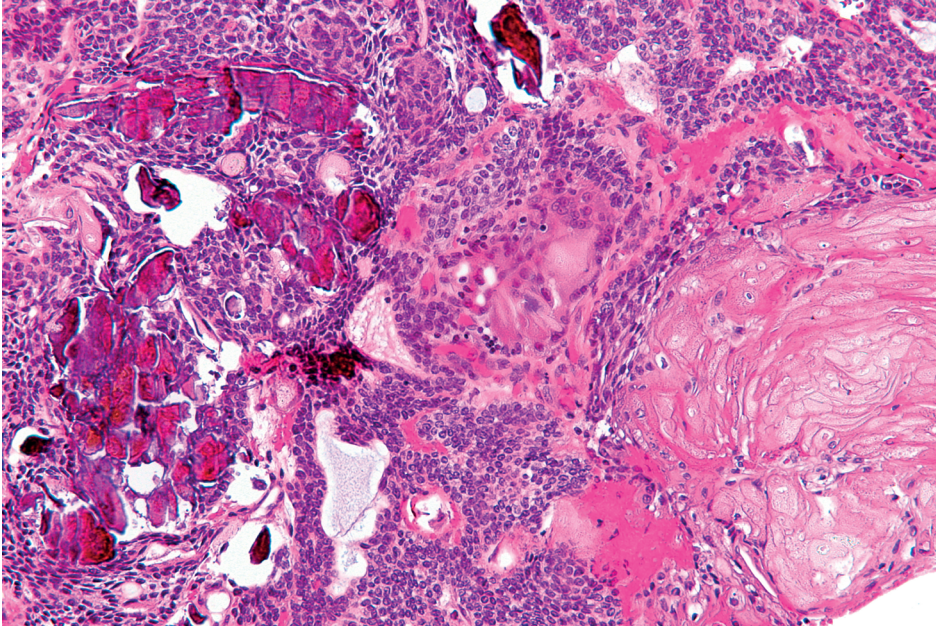


**A:** High magnification micrograph of an adamantinomatous craniopharyngioma (haematoxylin phloxine saffron [HPS] stain). Copyright © 2010 Michael Bonert.
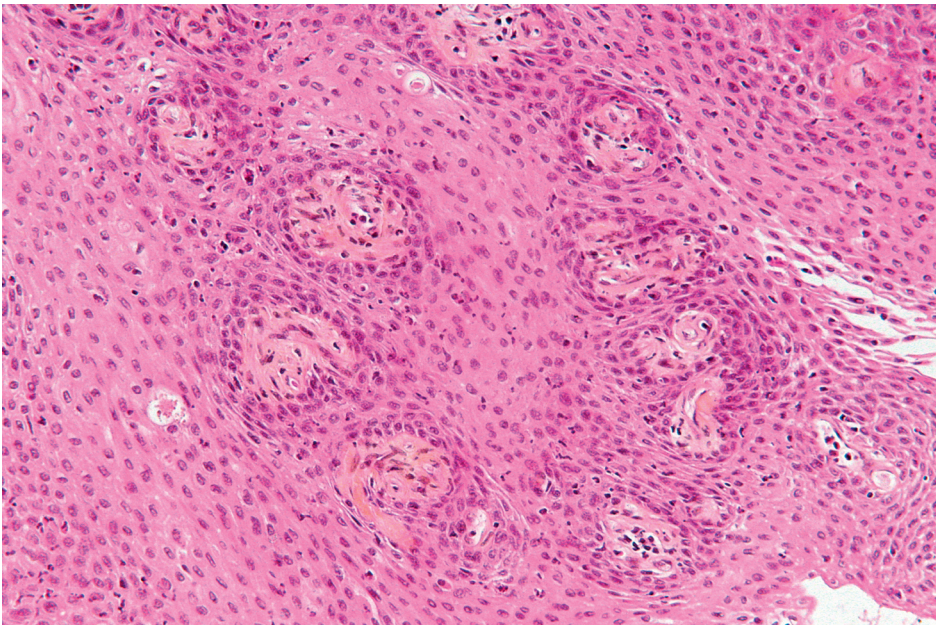


**B:** High magnification micrograph of a papillary craniopharyngioma (HPS stain). Copyright © 2011 Michael Bonert. Both figures can be found at https://commons.wikimedia.org/wiki/User:Nephron and are distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-sa/3.0/legalcode), which permits unrestricted use, distribution, and reproduction in any medium. The full text of this license can be found in this thesis at page 200.
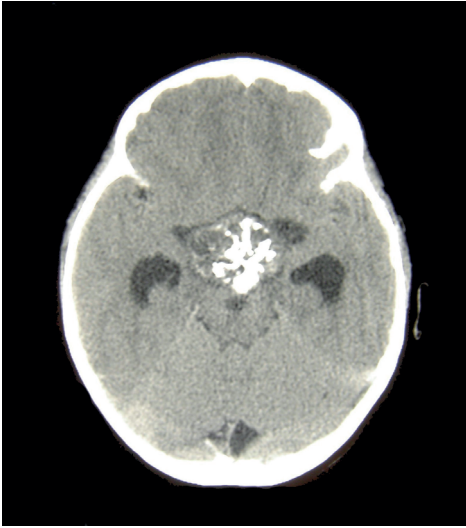
**Figure 1.6.** Unenhanced computed tomography of a craniopharyngioma
A calcified cystic structure can be seen in the suprasellar area, together with hydrocephalus. Reproduced from Garnett et al. *Orphanet Journal of Rare Diseases* Vol. **2**(18), 2007.[160] Copyright © 2007 BioMed Central Ltd. This figure is distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium.

sphenoidal (Figure 1.4C). The transsphenoidal approach is preferred for favourably localized, predominantly intrasellar, tumours, but requires an adequate pneumatization of the sphenoidal sinus. Otherwise, a transcranial resection may be carried out using a pterional, subfrontal, transcallosal, or transcortical-transventricular route.[87] In case radiotherapy is applied, the total recommended dose is 50-54 Gy, delivered in fractions of 1.8-2 Gy.[88] Craniopharyngioma treatment aims to provide long-term survival and disease control, while preserving quality of life by minimizing tumour- and treatment-related morbidity.

Although craniopharyngioma treatment is predominantly individualized based on tumour and patient characteristics, the preferred treatment strategy varies from centre to centre depending on local surgical and radiotherapeutic expertise.[87] Some centres favour initial gross total resection whereby preserving hypothalamic and optic functions,[83, 89-96] while other centres prefer subtotal resection or primary cyst drainage.[97-101] Gross total resection and subtotal resection with radiotherapy result in similar 5-year overall and recurrence-free survival rates. Overall and recurrence-free survival rates after subtotal resection without radiotherapy have been reported to be lower (Table 1.3).[81, 98, 102]

Treatment of recurrent craniopharyngioma is complicated by scarring from preceding surgery and radiotherapy, and depends on therapy previously administered.[103] The costs associated with a hospital admission for craniopharyngioma resection in the United States are estimated to be approximately $90 000.[104]

**Table 1.3.** Overall and recurrence-free survival after different craniopharyngioma treatment strategies

| Treatment strategy | 5-year overall survival (%) | 5-year recurrence-free survival (%) |
|---|---|---|
| Gross total resection | 82-100 | 60-100 |
| Subtotal resection with radiotherapy | 85-100 | 72-82 |
| Subtotal resection without radiotherapy | 75-90 | 25-47 |

Data from Karavitaki et al.[81], Schoenfeld et al.[98], and Rao et al.[102]

## Survival and long-term consequences of craniopharyngioma

Recent studies in patients with craniopharyngioma reported 10-year overall and recurrence-free survival rates between 40-95% and 44-76%, respectively.[83, 105-111] Despite these relatively encouraging survival rates, long-term tumour- and treatment-related health conditions are frequent,[83, 101, 106, 108, 110-116] and significantly impair quality of life.[112, 117-121] Pituitary hormone deficiencies, visual impairment, and obesity are the most common long-term health effects (Table 1.4).[101, 106, 111-116] In addition, neurocognitive and neurobehavioral deficits occur frequently, especially in patients with childhood-onset disease.[122-127] Moreover, specific late effects due to hypothalamic dysfunction have been reported (e.g. absence of thirst, loss of temperature control, sleep-wake disorders).[128-135]

Although many groups investigated long-term health conditions in patients with craniopharyngioma, most focused on patients treated with neurosurgical resection and radiotherapy solely.[83, 101, 106, 108-112, 114-116] Long-term sequelae of other treatment modalities, like $^{90}$Yttrium brachytherapy and primary cyst drainage, remain largely unknown. In addition, nearly all available studies have a relatively short follow-up period of less than ten years.[81, 83, 101, 107, 108, 110, 111, 113, 114] This precludes the assessment of long-term health conditions that require a prolonged time to develop (e.g. radiation-induced pituitary dysfunction).[136] Moreover, only a few reports evaluated long-term health effects in relation to the age at craniopharyngioma diagnosis (i.e. childhood- vs. adult-onset).[81, 112, 115] These studies reported inconclusive results.

Most studies on long-term tumour- and treatment-related sequelae in patients with craniopharyngioma have directly examined long-term health conditions. Alternatively, long-term health effects could be evaluated relative to the general population. To date, only few such studies have been performed. One study observed excess morbidity due to type 2 diabetes mellitus, fracture, infection, cerebral infarction, and visual impairment.[108] Six studies reported excess all-cause mortality.[108, 137-141] Three of these studies also evaluated cause-specific mortality, and observed a significantly increased risk for mortality due to circulatory and respiratory diseases.[108, 137, 138] Only a minority of these studies examined risk factors for excess morbidity and mortality.[108, 137, 139]

Obesity due to hypothalamic damage is one of the most important long-term health conditions in patients with craniopharyngioma. Hypothalamic damage may result in acquired leptin and insulin resistance, as well as autonomic nervous system dysfunc-

**Table 1.4.** Long-term health conditions in patients with craniopharyngioma

| Long-term health conditions | All patients (%) | Children (%) | Adults (%) |
| --- | --- | --- | --- |
| Visual acuity disorder | 49 | 52 | 48 |
| Visual field defect | 49 | 52-58 | 48-64 |
| Obesity | 11-43 | 11-46 | 15-52 |
| Epilepsy | 19 | 7-25 | 16 |
| Neurological deficit | 2-9 | 5-18 | 2-5 |
| Growth hormone deficiency | 66-94 | 66-94 | NA |
| Hypogonadotropic hypogonadism | 95 | 77-97 | 68-94 |
| Secondary adrenal insufficiency | 46-89 | 59-94 | 39-90 |
| Secondary hypothyroidism | 55-93 | 47-99 | 64-92 |
| Diabetes insipidus | 62-76 | 61-89 | 64-68 |
| Panhypopituitarism | 59 | 57-58 | 60 |

NA = not available. Data from Kendall-Taylor et al.[112], Sughrue et al.[113], Elliott et al.[114], Gautier et al.[115], Lopez-Serna et al.[106], Yuen et al.[116], Tan et al.[101], and Shi et al.[111]

tion, which may altogether adversely affect food intake, metabolism, and energy expenditure.[142] Other factors, like a familial predisposition for obesity, physical inactivity, increased daytime sleepiness, and psychological difficulties may also contribute to excessive weight gain.[117, 143, 144] Obesity develops predominantly during the first twelve years after craniopharyngioma treatment.[109] In this twelve years, the most significant weight gain occurs during the first year.[145] Obesity is the main predictor for a worse quality of life in patients with craniopharyngioma.[112, 117, 118, 120, 121]

As indicated above, obesity is often associated with other metabolic abnormalities, like the components of the metabolic syndrome.[52] To date, only a few studies investigated the metabolic syndrome and its components in patients with craniopharyngioma.[139, 146-150] Small study populations that mainly consisted of children, a lack of comparison to control data, and the evaluation of only a few risk factors for the metabolic syndrome and its components were major limitations of these studies.

Treatment of obesity in patients with craniopharyngioma is difficult. Lifestyle modification and pharmacotherapy have only modest effects.[142, 151-153] Therefore, bariatric surgery has been proposed.[154] However, there are concerns regarding the safety of bariatric procedures in this patient population, since drug absorption and bioavailability may be affected.[155, 156] To date, only a few studies investigated the efficacy of bariatric surgery regarding its effects on weight loss in patients with craniopharyngioma.[157-159] However, none studied weight loss relatively to matched control subjects. In addition, only one study evaluated the effects on hormone replacement therapy requirements.[159]

In Figure 1.7, current knowledge of long-term endocrine and metabolic consequences of cancer treatment in patients with craniopharyngioma is summarized.

**Figure 1.7.** Current knowledge of long-term endocrine and metabolic consequences of cancer treatment in patients with craniopharyngioma
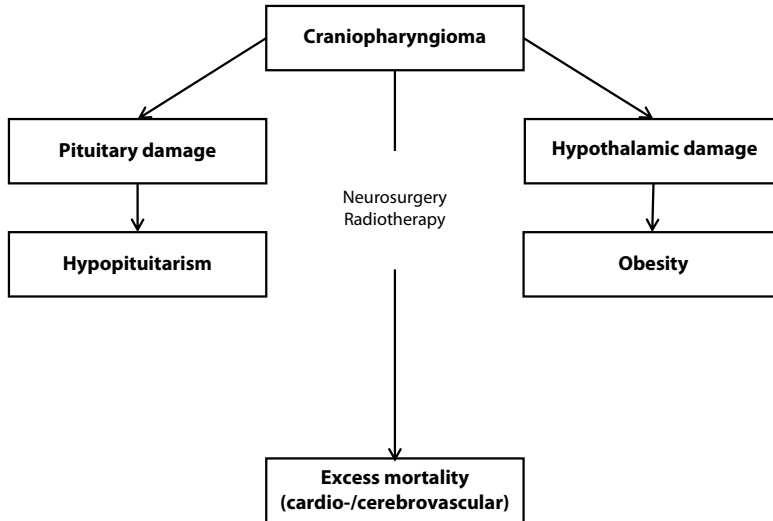


## AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis was to examine long-term endocrine and metabolic conditions, as well as their determinants in patients treated for cancer with a special focus on patients treated for craniopharyngioma. **Chapter 1** provides an introduction into cancer, cancer survival, and long-term endocrine and metabolic consequences of cancer and its treatment, as well as an overview of craniopharyngioma and its associated long-term health conditions. In **Chapter 2**, risk factors for subsequent endocrine-related cancer in childhood cancer survivors are reviewed. Thereby, there is a special focus on secondary neoplasms of the breast and thyroid. **Chapter 3** provides a study on daily life physical activity in survivors of nephroblastoma and neuroblastoma relative to a socio-demographically similar control group not treated for cancer. In **Chapter 4**, a large single-centre cohort of patients treated for craniopharyngioma is studied for long-term health conditions. In this chapter, long-term sequelae are evaluated according to the initial craniopharyngioma treatment strategy, as well as age group at craniopharyngioma diagnosis. **Chapter 5** provides a study in which morbidity and mortality in patients with craniopharyngioma are investigated relative to the general population. To increase the strength of this study and to replicate the findings in two study populations, we collaborated with the Sahlgrenska University Hospital in Gothenburg, Sweden. In **Chapter 6**, the metabolic syndrome and its components are studied in a large cohort of Dutch and Swedish patients with craniopharyngioma. **Chapter 7** provides a matched case-control

study in which the efficacy and safety of bariatric surgery in patients with craniopharyngioma are investigated relative to control subjects with common obesity. In **Chapter 8**, general discussion and conclusions of this thesis are presented.

## REFERENCES

1.  Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J & Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015 **65** 87-108.

2.  Ward E, DeSantis C, Robbins A, Kohler B & Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin* 2014 **64** 83-103.

3.  Steliarova-Foucher E, Colombet M, Ries LAG, Hesseling P, Moreno F, Shin HY & Stiller CA. International Incidence of Childhood Cancer, Volume III (electronic version). Lyon, France: International Agency for Research on Cancer, 2017.

4.  Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D & Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer, 2013.

5.  Van den Heuvel-Eibrink MM & Tissing WJE. Oncologie. In *Compendium Kindergeneeskunde*, ch. 32, pp 316-329. Houten: Bohn Stafleu van Loghum, 2011.

6.  Vineis P & Wild CP. Global cancer patterns: causes and prevention. *Lancet* 2014 **383** 549-557.

7.  Global Health Estimates 2015: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2015. Geneva: World Health Organization, 2016.

8.  World Health Organization, Department of Information, Evidence and Research. Mortality database. 2017.

9.  Colditz GA, Sellers TA & Trapido E. Epidemiology - identifying the causes and preventability of cancer? *Nat Rev Cancer* 2006 **6** 75-83.

10. Chabner BA & Roberts TG, Jr. Timeline: Chemotherapy and the war on cancer. *Nat Rev Cancer* 2005 **5** 65-72.

11. Lawrence TS, Haffty BG & Harris JR. Milestones in the use of combined-modality radiation therapy and chemotherapy. *J Clin Oncol* 2014 **32** 1173-1179.

12. Hudson MM, Link MP & Simone JV. Milestones in the curability of pediatric cancers. *J Clin Oncol* 2014 **32** 2391-2397.

13. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen WQ, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP & Group CW. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2015 **385** 977-1010.

14. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, Trama A, Visser O, Brenner H, Ardanaz E, Bielska-Lasota M, Engholm G, Nennecke A, Siesling S, Berrino F, Capocaccia R & Group E-W. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. *Lancet Oncol* 2014 **15** 23-34.

15. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, Dimitrova N, Jakab Z, Kaatsch P, Lacour B, Mallone S, Marcos-Gragera R, Minicozzi P, Sanchez-Perez MJ, Sant M, Santaquilani M, Stiller C, Tavilla A, Trama A, Visser O, Peris-Bonet R & Group EW. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. *Lancet Oncol* 2014 **15** 35-47.

16. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ & Cronin KA. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, 2017.

17. Mullan F. Seasons of survival: reflections of a physician with cancer. *N Engl J Med* 1985 **313** 270-273.

18.   *Institute of Medicine and National Research Council. From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington, DC: The National Academies Press, 2006.
19.   Hewitt M, Weiner SL & Simone JV. In *Childhood Cancer Survivorship: Improving Care and Quality of Life*. Washington (DC), 2003.
20.   Stein KD, Syrjala KL & Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer* 2008 **112** 2577-2592.
21.   Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W, Robison LL & Childhood Cancer Survivor S. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006 **355** 1572-1582.
22.   Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, Jaspers MW, Koning CC, Oldenburger F, Langeveld NE, Hart AA, Bakker PJ, Caron HN & van Leeuwen FE. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007 **297** 2705-2715.
23.   Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, Green DM, Armstrong GT, Nottage KA, Jones KE, Sklar CA, Srivastava DK & Robison LL. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA* 2013 **309** 2371-2381.
24.   Armstrong GT, Kawashima T, Leisenring W, Stratton K, Stovall M, Hudson MM, Sklar CA, Robison LL & Oeffinger KC. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. *J Clin Oncol* 2014 **32** 1218-1227.
25.   Harrison SE, Watson EK, Ward AM, Khan NF, Turner D, Adams E, Forman D, Roche MF & Rose PW. Primary health and supportive care needs of long-term cancer survivors: a questionnaire survey. *J Clin Oncol* 2011 **29** 2091-2098.
26.   Deckx L, van den Akker M, Metsemakers J, Knottnerus A, Schellevis F & Buntinx F. Chronic Diseases among Older Cancer Survivors. *J Cancer Epidemiol* 2012 **2012** 206414.
27.   Heins MJ, Korevaar JC, Hopman PE, Donker GA, Schellevis FG & Rijken MP. Health-related quality of life and health care use in cancer survivors compared with patients with chronic diseases. *Cancer* 2016 **122** 962-970.
28.   Smith AW, Reeve BB, Bellizzi KM, Harlan LC, Klabunde CN, Amsellem M, Bierman AS & Hays RD. Cancer, comorbidities, and health-related quality of life of older adults. *Health Care Financ Rev* 2008 **29** 41-56.
29.   Khan NF, Mant D, Carpenter L, Forman D & Rose PW. Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study. *Br J Cancer* 2011 **105 Suppl 1** S29-37.
30.   Cho H, Mariotto AB, Mann BS, Klabunde CN & Feuer EJ. Assessing non-cancer-related health status of US cancer patients: other-cause survival and comorbidity prevalence. *Am J Epidemiol* 2013 **178** 339-349.
31.   Gebauer J, Fick EM, Waldmann A, Langer T, Kreitschmann-Andermahr I, Lehnert H, Katalinic A & Brabant G. Self-reported endocrine late effects in adults treated for brain tumours, Hodgkin and non-Hodgkin lymphoma: a registry based study in Northern Germany. *Eur J Endocrinol* 2015 **173** 139-148.
32.   Cardous-Ubbink MC, Heinen RC, Langeveld NE, Bakker PJ, Voute PA, Caron HN & van Leeuwen FE. Long-term cause-specific mortality among five-year survivors of childhood cancer. *Pediatr Blood Cancer* 2004 **42** 563-573.

33.  Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL & Mertens AC. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol* 2009 **27** 2328-2338.

34.  Baade PD, Fritschi L & Eakin EG. Non-cancer mortality among people diagnosed with cancer (Australia). *Cancer Causes Control* 2006 **17** 287-297.

35.  Shin DW, Ahn E, Kim H, Park S, Kim YA & Yun YH. Non-cancer mortality among long-term survivors of adult cancer in Korea: national cancer registry study. *Cancer Causes Control* 2010 **21** 919-929.

36.  Prasad PK, Signorello LB, Friedman DL, Boice JD, Jr. & Pukkala E. Long-term non-cancer mortality in pediatric and young adult cancer survivors in Finland. *Pediatr Blood Cancer* 2012 **58** 421-427.

37.  Zhang Y, Goddard K, Spinelli JJ, Gotay C & McBride ML. Risk of Late Mortality and Second Malignant Neoplasms among 5-Year Survivors of Young Adult Cancer: A Report of the Childhood, Adolescent, and Young Adult Cancer Survivors Research Program. *J Cancer Epidemiol* 2012 **2012** 103032.

38.  Kero AE, Jarvela LS, Arola M, Malila N, Madanat-Harjuoja LM, Matomaki J & Lahteenmaki PM. Late mortality among 5-year survivors of early onset cancer: a population-based register study. *Int J Cancer* 2015 **136** 1655-1664.

39.  de Fine Licht S, Winther JF, Gudmundsdottir T, Holmqvist AS, Bonnesen TG, Asdahl PH, Tryggvadottir L, Anderson H, Wesenberg F, Malila N, Holm K, Hasle H, Olsen JH & group ALs. Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study. *Lancet* 2014 **383** 1981-1989.

40.  Fossa SD, Vassilopoulou-Sellin R & Dahl AA. Long term physical sequelae after adult-onset cancer. *J Cancer Surviv* 2008 **2** 3-11.

41.  Rose SR, Horne VE, Howell J, Lawson SA, Rutter MM, Trotman GE & Corathers SD. Late endocrine effects of childhood cancer. *Nat Rev Endocrinol* 2016 **12** 319-336.

42.  Shahrokni A, Wu AJ, Carter J & Lichtman SM. Long-term Toxicity of Cancer Treatment in Older Patients. *Clin Geriatr Med* 2016 **32** 63-80.

43.  Morton LM, Onel K, Curtis RE, Hungate EA & Armstrong GT. The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. *Am Soc Clin Oncol Educ Book* 2014 e57-67.

44.  Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL & Neglia JP. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2010 **102** 1083-1095.

45.  Chao C, Xu L, Bhatia S, Cooper R, Brar S, Wong FL & Armenian SH. Cardiovascular Disease Risk Profiles in Survivors of Adolescent and Young Adult (AYA) Cancer: The Kaiser Permanente AYA Cancer Survivors Study. *J Clin Oncol* 2016 **34** 1626-1633.

46.  Armenian SH, Xu L, Ky B, Sun C, Farol LT, Pal SK, Douglas PS, Bhatia S & Chao C. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. *J Clin Oncol* 2016 **34** 1122-1130.

47.  van Waas M, Neggers SJ, Pieters R & van den Heuvel-Eibrink MM. Components of the metabolic syndrome in 500 adult long-term survivors of childhood cancer. *Ann Oncol* 2010 **21** 1121-1126.

48.  van Waas M, Neggers SJ, van der Lelij AJ, Pieters R & van den Heuvel-Eibrink MM. The metabolic syndrome in adult survivors of childhood cancer, a review. *J Pediatr Hematol Oncol* 2010 **32** 171-179.

49.  de Haas EC, Oosting SF, Lefrandt JD, Wolffenbuttel BH, Sleijfer DT & Gietema JA. The metabolic syndrome in cancer survivors. *Lancet Oncol* 2010 **11** 193-203.

50. Jung HS, Myung SK, Kim BS & Seo HG. Metabolic syndrome in adult cancer survivors: a meta-analysis. *Diabetes Res Clin Pract* 2012 **95** 275-282.

51. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988 **37** 1595-1607.

52. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H & Eckel RH. The metabolic syndrome. *Endocr Rev* 2008 **29** 777-822.

53. Edwardson CL, Gorely T, Davies MJ, Gray LJ, Khunti K, Wilmot EG, Yates T & Biddle SJ. Association of sedentary behaviour with metabolic syndrome: a meta-analysis. *PLoS One* 2012 **7** e34916.

54. He D, Xi B, Xue J, Huai P, Zhang M & Li J. Association between leisure time physical activity and metabolic syndrome: a meta-analysis of prospective cohort studies. *Endocrine* 2014 **46** 231-240.

55. Stolley MR, Restrepo J & Sharp LK. Diet and physical activity in childhood cancer survivors: a review of the literature. *Ann Behav Med* 2010 **39** 232-249.

56. Demark-Wahnefried W, Rogers LQ, Alfano CM, Thomson CA, Courneya KS, Meyerhardt JA, Stout NL, Kvale E, Ganzer H & Ligibel JA. Practical clinical interventions for diet, physical activity, and weight control in cancer survivors. *CA Cancer J Clin* 2015 **65** 167-189.

57. Bray F, Ren JS, Masuyer E & Ferlay J. GLOBOCAN 2012 v1.0, Cancer Prevalence Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer, 2013.

58. Muller HL. Craniopharyngioma. *Endocr Rev* 2014 er20131115.

59. Von Zenker AF. Enorme Zystenbildung im Gehirn, vom Hirnanhang ausgehend. *Arch Pathol Anat Physiol Klin Med* 1857 **2** 454–466.

60. Erdheim J. Uber hypophysenganggeschwwuste und hirncholesteatome. Gerold, Wien, 1904.

61. Halstead AE. Remarks on the operative treatment of 256 tumors of the hypophysis. *Surg Gynecol Obstet* 1910 **10** 494–502.

62. Lewis DD. A contribution to the subject of tumors of the hypophysis. *JAMA* 1910 **55** 1002–1008.

63. Frazier CH & Alpers BJ. Adamantinoma of the craniopharyngeal duct. *Arch NeurPsych* 1931 **26** 905-965.

64. Cushing H. Intracranial Tumors. Charles C Thomas, Baltimore, 1932.

65. Nielsen EH, Feldt-Rasmussen U, Poulsgaard L, Kristensen LO, Astrup J, Jorgensen JO, Bjerre P, Andersen M, Andersen C, Jorgensen J, Lindholm J & Laurberg P. Incidence of craniopharyngioma in Denmark (n = 189) and estimated world incidence of craniopharyngioma in children and adults. *J Neurooncol* 2011 **104** 755-763.

66. Ostrom QT, Gittleman H, Xu J, Kromer C, Wolinsky Y, Kruchko C & Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009-2013. *Neuro Oncol* 2016 **18** v1-v75.

67. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F & Bruner JM. The descriptive epidemiology of craniopharyngioma. *J Neurosurg* 1998 **89** 547-551.

68. de Moraes DC, Vaisman M, Conceicao FL & Ortiga-Carvalho TM. Pituitary development: a complex, temporal regulated process dependent on specific transcriptional factors. *J Endocrinol* 2012 **215** 239-245.

69. Harwood-Nash DC. Neuroimaging of childhood craniopharyngioma. *Pediatr Neurosurg* 1994 **21** **Suppl 1** 2-10.

70. Lubuulwa J & Lei T. Pathological and Topographical Classification of Craniopharyngiomas: A Literature Review. *J Neurol Surg Rep* 2016 **77** e121-127.

71. Pekmezci M, Louie J, Gupta N, Bloomer MM & Tihan T. Clinicopathological characteristics of adamantinomatous and papillary craniopharyngiomas: University of California, San Francisco experience 1985-2005. *Neurosurgery* 2010 **67** 1341-1349; discussion 1349.

72. Goldberg GM & Eshbaugh DE. Squamous cell nests of the pituitary gland as related to the origin of craniopharyngiomas. A study of their presence in the newborn and infants up to age four. *Arch Pathol* 1960 **70** 293-299.

73. Hunter IJ. Squamous metaplasia of cells of the anterior pituitary gland. *J Pathol Bacteriol* 1955 **69** 141-145.

74. Sekine S, Shibata T, Kokubu A, Morishita Y, Noguchi M, Nakanishi Y, Sakamoto M & Hirohashi S. Craniopharyngiomas of adamantinomatous type harbor beta-catenin gene mutations. *Am J Pathol* 2002 **161** 1997-2001.

75. Andoniadou CL, Gaston-Massuet C, Reddy R, Schneider RP, Blasco MA, Le Tissier P, Jacques TS, Pevny LH, Dattani MT & Martinez-Barbera JP. Identification of novel pathways involved in the pathogenesis of human adamantinomatous craniopharyngioma. *Acta Neuropathol* 2012 **124** 259-271.

76. Brastianos PK, Taylor-Weiner A, Manley PE, Jones RT, Dias-Santagata D, Thorner AR, Lawrence MS, Rodriguez FJ, Bernardo LA, Schubert L, Sunkavalli A, Shillingford N, Calicchio ML, Lidov HG, Taha H, Martinez-Lage M, Santi M, Storm PB, Lee JY, Palmer JN, Adappa ND, Scott RM, Dunn IF, Laws ER, Jr., Stewart C, Ligon KL, Hoang MP, Van Hummelen P, Hahn WC, Louis DN, Resnick AC, Kieran MW, Getz G & Santagata S. Exome sequencing identifies BRAF mutations in papillary craniopharyngiomas. *Nat Genet* 2014 **46** 161-165.

77. Vargas JR, Pino JA & Murad TM. Craniopharyngioma in two siblings. *JAMA* 1981 **246** 1807-1808.

78. Combelles G, Ythier H, Wemeau JL, Cappoen JP, Delandsheer JM & Christiaens JL. [Craniopharyngioma in the same family]. *Neurochirurgie* 1984 **30** 347-349.

79. Boch AL, van Effenterre R & Kujas M. Craniopharyngiomas in two consanguineous siblings: case report. *Neurosurgery* 1997 **41** 1185-1187.

80. Green AL, Yeh JS & Dias PS. Craniopharyngioma in a mother and daughter. *Acta Neurochir (Wien)* 2002 **144** 403-404.

81. Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, Shine B, Turner HE & Wass JA. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol (Oxf)* 2005 **62** 397-409.

82. Nielsen EH, Jorgensen JO, Bjerre P, Andersen M, Andersen C, Feldt-Rasmussen U, Poulsgaard L, Kristensen LO, Astrup J, Jorgensen J & Laurberg P. Acute presentation of craniopharyngioma in children and adults in a Danish national cohort. *Pituitary* 2013 **16** 528-535.

83. Du C, Feng CY, Yuan XR, Liu Q, Peng ZF, Jiang XJ, Li XJ, Xiao GL, Li YF & Xiong T. Microsurgical Management of Craniopharyngiomas via a Unilateral Subfrontal Approach: A Retrospective Study of 177 Continuous Cases. *World Neurosurg* 2016 **90** 454-468.

84. Muller HL, Emser A, Faldum A, Bruhnken G, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R & Sorensen N. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. *J Clin Endocrinol Metab* 2004 **89** 3298-3305.

85. Buchfelder M & Schlaffer S. Imaging of pituitary pathology. *Handb Clin Neurol* 2014 **124** 151-166.

86. Karavitaki N. Management of craniopharyngiomas. *J Endocrinol Invest* 2014 **37** 219-228.

87. Buchfelder M, Schlaffer SM, Lin F & Kleindienst A. Surgery for craniopharyngioma. *Pituitary* 2013 **16** 18-25.

88. Iannalfi A, Fragkandrea I, Brock J & Saran F. Radiotherapy in craniopharyngiomas. *Clin Oncol (R Coll Radiol)* 2013 **25** 654-667.

89. Mortini P, Losa M, Pozzobon G, Barzaghi R, Riva M, Acerno S, Angius D, Weber G, Chiumello G & Giovanelli M. Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series. *J Neurosurg* 2011 **114** 1350-1359.

90.  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. *J Neurosurg Pediatr* 2010 **5** 30-48.

91.  Zhang YQ, Ma ZY, Wu ZB, Luo SQ & Wang ZC. Radical resection of 202 pediatric craniopharyngiomas with special reference to the surgical approaches and hypothalamic protection. *Pediatr Neurosurg* 2008 **44** 435-443.

92.  Bal E, Oge K & Berker M. Endoscopic Endonasal Transsphenoidal Surgery, a Reliable Method for Treating Primary and Recurrent/Residual Craniopharyngiomas: Nine Years of Experience. *World Neurosurg* 2016.

93.  Xing H, Xing H, Hui P & Yang B. Removal of craniopharyngioma via fronto-basal interhemispheric approach. *Oncol Lett* 2016 **12** 147-149.

94.  Cheng J, Shao Q, Pan Z & You J. Analysis and Long-Term Follow-Up of the Surgical Treatment of Children With Craniopharyngioma. *J Craniofac Surg* 2016 **27** e763-e766.

95.  Moussazadeh N, Prabhu V, Bander ED, Cusic RC, Tsiouris AJ, Anand VK & Schwartz TH. Endoscopic endonasal versus open transcranial resection of craniopharyngiomas: a case-matched single-institution analysis. *Neurosurg Focus* 2016 **41** E7.

96.  Morisako H, Goto T, Goto H, Bohoun CA, Tamrakar S & Ohata K. Aggressive surgery based on an anatomical subclassification of craniopharyngiomas. *Neurosurg Focus* 2016 **41** E10.

97.  Winkfield KM, Tsai HK, Yao X, Larson E, Neuberg D, Pomeroy SL, Ullrich NJ, Cohen LE, Kieran MW, Scott RM, Goumnerova LC & Marcus KJ. Long-term clinical outcomes following treatment of childhood craniopharyngioma. *Pediatr Blood Cancer* 2011 **56** 1120-1126.

98.  Schoenfeld A, Pekmezci M, Barnes MJ, Tihan T, Gupta N, Lamborn KR, Banerjee A, Mueller S, Chang S, Berger MS & Haas-Kogan D. The superiority of conservative resection and adjuvant radiation for craniopharyngiomas. *J Neurooncol* 2012 **108** 133-139.

99.  Schubert T, Trippel M, Tacke U, van Velthoven V, Gumpp V, Bartelt S, Ostertag C & Nikkhah G. Neurosurgical treatment strategies in childhood craniopharyngiomas: is less more? *Childs Nerv Syst* 2009 **25** 1419-1427.

100.  Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, Zerah M, Bezerra M, Renier D, Pierre-Kahn A & Sainte-Rose C. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. *J Neurosurg* 2007 **106** 3-12.

101.  Tan TS, Patel L, Gopal-Kothandapani JS, Ehtisham S, Ikazoboh EC, Hayward R, Aquilina K, Skae M, Thorp N, Pizer B, Didi M, Mallucci C, Blair JC, Gaze MN, Kamaly-Asl I, Spoudeas H & Clayton PE. The neuroendocrine sequelae of paediatric craniopharyngioma: a 40 year meta-data analysis of 185 cases from three UK centres. *Eur J Endocrinol* 2017.

102.  Rao YJ, Hassanzadeh C, Fischer-Valuck B, Chicoine MR, Kim AH, Perkins SM & Huang J. Patterns of care and treatment outcomes of patients with Craniopharyngioma in the national cancer database. *J Neurooncol* 2016.

103.  Liubinas SV, Munshey AS & Kaye AH. Management of recurrent craniopharyngioma. *J Clin Neurosci* 2011 **18** 451-457.

104.  Zaidi HA, Chapple K & Little AS. National treatment trends, complications, and predictors of in-hospital charges for the surgical management of craniopharyngiomas in adults from 2007 to 2011. *Neurosurg Focus* 2014 **37** E6.

105.  Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, Bates AS & Stewart PM. Mortality in patients with pituitary disease. *Endocr Rev* 2010 **31** 301-342.

106. Lopez-Serna R, Gomez-Amador JL, Barges-Coll J, Nathal-Vera E, Revuelta-Gutierrez R, Alonso-Vanegas M, Ramos-Peek M & Portocarrero-Ortiz L. Treatment of craniopharyngioma in adults: systematic analysis of a 25-year experience. *Arch Med Res* 2012 **43** 347-355.

107. Lee CC, Yang HC, Chen CJ, Hung YC, Wu HM, Shiau CY, Guo WY, Pan DH, Chung WY & Liu KD. Gamma Knife surgery for craniopharyngioma: report on a 20-year experience. *J Neurosurg* 2014 **121 Suppl** 167-178.

108. 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. *J Clin Endocrinol Metab* 2015 **100** 467-474.

109. 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** 1029-1038.

110. Pan J, Qi S, Liu Y, Lu Y, Peng J, Zhang X, Xu Y, Huang GL & Fan J. Growth patterns of craniopharyngiomas: clinical analysis of 226 patients. *J Neurosurg Pediatr* 2016 **17** 418-433.

111. Shi X, Zhou Z, Wu B, Zhang Y, Qian H, Sun Y, Yang Y, Yu Z, Tang Z & Lu S. Outcome of Radical Surgical Resection for Craniopharyngioma with Hypothalamic Preservation: A Single-Center, Retrospective Study of 1054 Patients. *World Neurosurg* 2017.

112. Kendall-Taylor P, Jonsson PJ, Abs R, Erfurth EM, Koltowska-Haggstrom M, Price DA & Verhelst J. 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** 557-567.

113. Sughrue ME, Yang I, Kane AJ, Fang S, Clark AJ, Aranda D, Barani IJ & Parsa AT. Endocrinologic, neurologic, and visual morbidity after treatment for craniopharyngioma. *J Neurooncol* 2011 **101** 463-476.

114. Elliott RE, Jane JA, Jr. & Wisoff JH. Surgical management of craniopharyngiomas in children: meta-analysis and comparison of transcranial and transsphenoidal approaches. *Neurosurgery* 2011 **69** 630-643; discussion 643.

115. Gautier A, Godbout A, Grosheny C, Tejedor I, Coudert M, Courtillot C, Jublanc C, De Kerdanet M, Poirier JY, Riffaud L, Sainte-Rose C, Van Effenterre R, Brassier G, Bonnet F, Touraine P & Craniopharyngioma Study G. Markers of recurrence and long-term morbidity in craniopharyngioma: a systematic analysis of 171 patients. *J Clin Endocrinol Metab* 2012 **97** 1258-1267.

116. Yuen KC, Koltowska-Haggstrom M, Cook DM, Fox JL, Jonsson PJ, Geffner ME & Abs R. Primary treatment regimen and diabetes insipidus as predictors of health outcomes in adults with childhood-onset craniopharyngioma. *J Clin Endocrinol Metab* 2014 **99** 1227-1235.

117. Muller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, Korinthenberg R, Bettendorf M, Kuhl J, Gutjahr P, Sorensen N & Calaminus G. Obesity after childhood craniopharyngioma--German multicenter study on pre-operative risk factors and quality of life. *Klin Padiatr* 2001 **213** 244-249.

118. Muller HL, Faldum A, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R & Sorensen N. Functional capacity, obesity and hypothalamic involvement: cross-sectional study on 212 patients with childhood craniopharyngioma. *Klin Padiatr* 2003 **215** 310-314.

119. Dekkers OM, Biermasz NR, Smit JW, Groot LE, Roelfsema F, Romijn JA & Pereira AM. Quality of life in treated adult craniopharyngioma patients. *Eur J Endocrinol* 2006 **154** 483-489.

120. Patel KS, Raza SM, McCoul ED, Patrona A, Greenfield JP, Souweidane MM, Anand VK & Schwartz TH. Long-term quality of life after endonasal endoscopic resection of adult craniopharyngiomas. *J Neurosurg* 2015 **123** 571-580.

121. Yano S, Kudo M, Hide T, Shinojima N, Makino K, Nakamura H & Kuratsu J. Quality of Life and Clinical Features of Long-Term Survivors Surgically Treated for Pediatric Craniopharyngioma. *World Neurosurg* 2016 **85** 153-162.

122. Ozyurt J, Muller HL & Thiel CM. A systematic review of cognitive performance in patients with childhood craniopharyngioma. *J Neurooncol* 2015 **125** 9-21.

123. Fournier-Goodnight AS, Ashford JM, Merchant TE, Boop FA, Indelicato DJ, Wang L, Zhang H & Conklin HM. Neurocognitive functioning in pediatric craniopharyngioma: performance before treatment with proton therapy. *J Neurooncol* 2017.

124. Honegger J, Barocka A, Sadri B & Fahlbusch R. Neuropsychological results of craniopharyngioma surgery in adults: a prospective study. *Surg Neurol* 1998 **50** 19-28; discussion 28-19.

125. Donnet A, Schmitt A, Dufour H & Grisoli F. Neuropsychological follow-up of twenty two adult patients after surgery for craniopharyngioma. *Acta Neurochir (Wien)* 1999 **141** 1049-1054.

126. 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** e76562.

127. Flynn FG, Cummings JL & Tomiyasu U. Altered behavior associated with damage to the ventromedial hypothalamus: a distinctive syndrome. *Behav Neurol* 1988 **1** 49-58.

128. Smith D, Finucane F, Phillips J, Baylis PH, Finucane J, Tormey W & Thompson CJ. Abnormal regulation of thirst and vasopressin secretion following surgery for craniopharyngioma. *Clin Endocrinol (Oxf)* 2004 **61** 273-279.

129. de Vetten L & Bocca G. Systemic effects of hypothermia due to hypothalamic dysfunction after resection of a craniopharyngioma: case report and review of literature. *Neuropediatrics* 2013 **44** 159-162.

130. Zoli M, Sambati L, Milanese L, Foschi M, Faustini-Fustini M, Marucci G, de Biase D, Tallini G, Cecere A, Mignani F, Sturiale C, Frank G, Pasquini E, Cortelli P, Mazzatenta D & Provini F. Postoperative outcome of body core temperature rhythm and sleep-wake cycle in third ventricle craniopharyngiomas. *Neurosurg Focus* 2016 **41** E12.

131. van der Klaauw AA, Biermasz NR, Pereira AM, van Kralingen KW, Dekkers OM, Rabe KF, Smit JW & Romijn JA. Patients cured from craniopharyngioma or nonfunctioning pituitary macroadenoma (NFMA) suffer similarly from increased daytime somnolence despite normal sleep patterns compared to healthy controls. *Clin Endocrinol (Oxf)* 2008 **69** 769-774.

132. Muller HL. Increased daytime sleepiness in patients with childhood craniopharyngioma and hypothalamic tumor involvement: review of the literature and perspectives. *Int J Endocrinol* 2010 **2010** 519607.

133. Crowley RK, Woods C, Fleming M, Rogers B, Behan LA, O'Sullivan EP, Kane T, Agha A, Smith D, Costello RW & Thompson CJ. Somnolence in adult craniopharyngioma patients is a common, heterogeneous condition that is potentially treatable. *Clin Endocrinol (Oxf)* 2011 **74** 750-755.

134. Pickering L, Jennum P, Gammeltoft S, Poulsgaard L, Feldt-Rasmussen U & Klose M. Sleep-wake and melatonin pattern in craniopharyngioma patients. *Eur J Endocrinol* 2014 **170** 873-884.

135. Foschi M, Sambati L, Zoli M, Pierangeli G, Cecere A, Mignani F, Barletta G, Sturiale C, Faustini-Fustini M, Milanese L, Cortelli P, Mazzatenta D & Provini F. Site and type of craniopharyngiomas impact differently on 24-hour circadian rhythms and surgical outcome. A neurophysiological evaluation. *Auton Neurosci* 2017.

136. Darzy KH & Shalet SM. Hypopituitarism following Radiotherapy Revisited. *Endocr Dev* 2009 **15** 1-24.

137. Bulow B, Attewell R, Hagmar L, Malmstrom P, Nordstrom CH & Erfurth EM. Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumor recurrence. *J Clin Endocrinol Metab* 1998 **83** 3897-3904.

138. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC & Stewart PM. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet* 2001 **357** 425-431.

139. Pereira AM, Schmid EM, Schutte PJ, Voormolen JH, Biermasz NR, van Thiel SW, Corssmit EP, Smit JW, Roelfsema F & Romijn JA. High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. *Clin Endocrinol (Oxf)* 2005 **62** 197-204.

140. Crowley RK, Hamnvik OP, O'Sullivan EP, Behan LA, Smith D, Agha A & Thompson CJ. Morbidity and mortality in patients with craniopharyngioma after surgery. *Clin Endocrinol (Oxf)* 2010 **73** 516-521.

141. Gaillard RC, Mattsson AF, Akerblad AC, Bengtsson BA, Cara J, Feldt-Rasmussen U, Koltowska-Haggstrom M, Monson JP, Saller B, Wilton P & Abs R. Overall and cause-specific mortality in GH-deficient adults on GH replacement. *Eur J Endocrinol* 2012 **166** 1069-1077.

142. 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** 1774-1797.

143. Muller HL. Craniopharyngioma and hypothalamic injury: latest insights into consequent eating disorders and obesity. *Curr Opin Endocrinol Diabetes Obes* 2016 **23** 81-89.

144. Roemmler-Zehrer J, Geigenberger V, Stormann S, Ising M, Pfister H, Sievers C, Stalla GK & Schopohl J. Specific behaviour, mood and personality traits may contribute to obesity in patients with craniopharyngioma. *Clin Endocrinol (Oxf)* 2015 **82** 106-114.

145. Roth CL, Eslamy H, Werny D, Elfers C, Shaffer ML, Pihoker C, Ojemann J & Dobyns WB. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. *Obesity (Silver Spring)* 2015 **23** 1226-1233.

146. Holmer H, Ekman B, Bjork J, Nordstom CH, Popovic V, Siversson A & Erfurth EM. Hypothalamic involvement predicts cardiovascular risk in adults with childhood onset craniopharyngioma on long-term GH therapy. *Eur J Endocrinol* 2009 **161** 671-679.

147. 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** 364-370.

148. Profka E, Giavoli C, Bergamaschi S, Ferrante E, Malchiodi E, Sala E, Verrua E, Rodari G, Filopanti M, Beck-Peccoz P & Spada A. Analysis of short- and long-term metabolic effects of growth hormone replacement therapy in adult patients with craniopharyngioma and non-functioning pituitary adenoma. *J Endocrinol Invest* 2015 **38** 413-420.

149. Sahakitrungruang T, Klomchan T, Supornsilchai V & Wacharasindhu S. Obesity, metabolic syndrome, and insulin dynamics in children after craniopharyngioma surgery. *Eur J Pediatr* 2011 **170** 763-769.

150. Ferrau F, Spagnolo F, Cotta OR, Cannavo L, Alibrandi A, Russo GT, Aversa T, Trimarchi F & Cannavo S. Visceral adiposity index as an indicator of cardiometabolic risk in patients treated for craniopharyngioma. *Endocrine* 2016.

151. 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** 1768-1774.

152.  Steele CA, Cuthbertson DJ, MacFarlane IA, Javadpour M, Das KS, Gilkes C, Wilding JP & Daousi C. Hypothalamic obesity: prevalence, associations and longitudinal trends in weight in a specialist adult neuroendocrine clinic. *Eur J Endocrinol* 2013 **168** 501-507.

153.  Wang KW, Chau R, Fleming A, Banfield L, Singh SK, Johnston DL, Zelcer SM, Rassekh SR, Burrow S, Valencia M, de Souza RJ, Thabane L & Samaan MC. The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. *Obes Rev* 2017 **18** 899-914.

154.  Inge TH, Pfluger P, Zeller M, Rose SR, Burget L, Sundararajan S, Daniels SR & Tschop MH. Gastric bypass surgery for treatment of hypothalamic obesity after craniopharyngioma therapy. *Nat Clin Pract Endocrinol Metab* 2007 **3** 606-609.

155.  Padwal R, Brocks D & Sharma AM. A systematic review of drug absorption following bariatric surgery and its theoretical implications. *Obes Rev* 2010 **11** 41-50.

156.  Knibbe CA, Brill MJ, van Rongen A, Diepstraten J, van der Graaf PH & Danhof M. Drug disposition in obesity: toward evidence-based dosing. *Annu Rev Pharmacol Toxicol* 2015 **55** 149-167.

157.  Bretault M, Boillot A, Muzard L, Poitou C, Oppert JM, Barsamian C, Gatta B, Muller H, Weismann D, Rottembourg D, Inge T, Veyrie N, Carette C & Czernichow S. Clinical review: Bariatric surgery following treatment for craniopharyngioma: a systematic review and individual-level data meta-analysis. *J Clin Endocrinol Metab* 2013 **98** 2239-2246.

158.  Bretault M, Laroche S, Lacorte JM, Barsamian C, Polak M, Raffin-Sanson ML, Touraine P, Bouillot JL, Czernichow S & Carette C. Postprandial GLP-1 Secretion After Bariatric Surgery in Three Cases of Severe Obesity Related to Craniopharyngiomas. *Obes Surg* 2016.

159.  Wolf P, Winhofer Y, Smajis S, Kruschitz R, Schindler K, Gessl A, Riedl M, Vila G, Raber W, Langer F, Prager G, Ludvik B, Luger A & Krebs M. Hormone Substitution after Gastric Bypass Surgery in Patients with Hypopituitarism Secondary to Craniopharyngioma. *Endocr Pract* 2016.

160.  Garnett MR, Puget S, Grill J & Sainte-Rose C. Craniopharyngioma. *Orphanet J Rare Dis* 2007 **2** 18.

# Chapter 2

## Risk factors for subsequent endocrine-related cancer in childhood cancer survivors

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## ABSTRACT

Long-term adverse health conditions, including secondary malignant neoplasms, are common in childhood cancer survivors. Although mortality attributable to secondary malignancies declined over the past decades, the risk for developing a solid secondary malignant neoplasm did not. Endocrine-related malignancies are among the most common secondary malignant neoplasms observed in childhood cancer survivors. In this systematic review, we describe risk factors for secondary malignant neoplasms of the breast and thyroid, since these are the most common secondary endocrine-related malignancies in childhood cancer survivors. Radiotherapy is the most important risk factor for secondary breast and thyroid cancer in childhood cancer survivors. Breast cancer risk is especially increased in survivors of Hodgkin lymphoma who received moderate- to high-dosed mantle field irradiation. Recent studies also demonstrated an increased risk after lower-dosed irradiation in other radiation fields for other childhood cancer subtypes. Premature ovarian insufficiency may protect against radiation-induced breast cancer. Although evidence is weak, oestrogen-progestin replacement therapy does not seem to be associated with an increased breast cancer risk in premature ovarian insufficient childhood cancer survivors. Radiotherapy involving the thyroid gland increases the risk for secondary differentiated thyroid carcinoma, as well as benign thyroid nodules. Currently available studies on secondary malignant neoplasms in childhood cancer survivors are limited by short follow-up durations and assessed prior treatment regimens. In addition, studies on risk-modifying effects of environmental and lifestyle factors are lacking. Risk-modifying effects of premature ovarian insufficiency and oestrogen-progestin replacement therapy on radiation-induced breast cancer require further study.

## INTRODUCTION

Childhood cancer survival has increased substantially over the past five decades due to advances in therapy, risk-based treatment stratification, and supportive care.[1] To date, approximately 80% of children and adolescents survive at least five years following a diagnosis of childhood cancer,[2, 3] and are thereby subsequently considered childhood cancer survivors. This percentage is anticipated to grow due to further improvements in childhood cancer care,[1] and a slow increase in childhood cancer incidence as reported by some investigators.[4, 5] Accordingly, awareness of and insight in side effects and long-term consequences of childhood cancer treatment have become increasingly important.[6-11] At an attained age of 45 years, approximately 95% of childhood cancer survivors suffer from at least one chronic health condition related to their former cancer treatment; in approximately 75% this concerns a serious/disabling or life-threatening condition.[9] Over the past decades, childhood cancer treatment protocols have been modified, aiming to reduce the occurrence and severity of long-term treatment-related complications. Recently, Armstrong et al. demonstrated that these efforts resulted in improved long-term survival.[12]

Secondary neoplasms are among the most serious long-term adverse health conditions in childhood cancer survivors, and can be defined as histologically distinct tumours developing after primary cancer therapy. They have been estimated to affect approximately 21% of childhood cancer survivors after 30 years of follow-up since primary cancer diagnosis.[13] This estimation includes both benign and malignant secondary neoplasms. The 30-year cumulative incidence of secondary malignant neoplasms solely is approximately 8%, and represents a six-fold increased risk in comparison to the general population.[13] The increased risk for secondary malignancies in childhood cancer survivors seems to persist even after 40 years of follow-up since primary cancer diagnosis.[14] At an attained survivor's age of 60 years, the cumulative incidence of secondary malignant neoplasms varies between 14-18%.[14, 15] The risk for secondary malignant neoplasms in older childhood cancer survivors remains unknown. Although most secondary malignant neoplasms are diagnosed during the first 10-20 years following childhood cancer treatment,[13, 16] they may present within months to decades following the completion of former cancer therapy.[16] Risk factors for the development of secondary malignancies in childhood cancer survivors include host factors, primary cancer diagnosis, types and timing of primary cancer treatment, environmental factors, and lifestyle factors.[17] Secondary malignant neoplasms appear to be an important cause of death in childhood cancer survivors. Recent cohort studies demonstrated that 12-19% of mortality in individuals who survived at least five years following a diagnosis of childhood cancer was attributable to secondary malignancies.[18-20] After 25 years of follow-up since primary cancer diagnosis, secondary malignant neoplasms even become the most

important cause of death in survivors of childhood cancer.[18, 20] Although mortality attributable to secondary malignancies in childhood cancer survivors declined over the past treatment eras,[12] the risk for developing a solid secondary malignant neoplasm did not.[21] Endocrine-related cancers are among the most common secondary malignancies in childhood cancer survivors.[13-15, 22] In the Childhood Cancer Survivor Study they represent 40% of the invasive secondary malignant neoplasms observed (Figure 2.1A).[13]

In this review, we will discuss risk factors for secondary endocrine-related malignant neoplasms in childhood cancer survivors. A special focus will be on breast and thyroid cancer, since these are the most common secondary endocrine-related malignancies in survivors of childhood cancer.[13-15]

## SEARCH STRATEGY

We systematically searched the MEDLINE-database (United States National Library of Medicine, Washington, DC) until January 2016 for relevant articles on secondary cancer risk in survivors of paediatric malignancies. The keywords "childhood cancer survivors", "second malignant neoplasms", "secondary malignant neoplasms", "subsequent neoplasms", "endocrine cancers", "breast cancer", "thyroid cancer", "risk factors", "radiotherapy", "radiation", "irradiation", "chemotherapy", "stem cell transplantation", "total body irradiation", "conformal radiotherapy", "intensity-modulated radiation therapy", and "proton-beam therapy" were used. Only articles written in English were included in the review. Reference lists of included articles were checked for additional relevant publications. In case two or more articles described the same patient cohort, the most recent or relevant article was included.

## RISK FACTORS FOR SECONDARY MALIGNANT NEOPLASMS IN CHILDHOOD CANCER SURVIVORS

In the Childhood Cancer Survivor Study, host-, disease-, and treatment-related risk factors for the development of secondary neoplasms in childhood cancer survivors have been identified.[13] The Childhood Cancer Survivor Study is a multi-institutional study conducted in the United States and Canada, and involves 14 363 individuals treated for cancer < 21 years of age.[23] Female gender and older age at initial cancer diagnosis were associated with an increased risk for secondary malignant neoplasms after childhood cancer (relative risk [RR] 1.4 [95% confidence interval (CI) 1.2-1.6] for females vs. males; RR 1.5 [95% CI 1.2-1.9] for age at diagnosis ≥ 15 years vs. 0-4 years).[13] The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) of

the United States could not demonstrate this sex difference in the risk for secondary malignant neoplasms, but found a somewhat higher risk for secondary malignancies in black vs. white people (standardized incidence ratio [SIR] 8.9 vs. SIR 5.5; excess absolute risk [EAR] 18.4 vs. 15.0 per 10 000 person-years).[22] Genetic susceptibility might contribute to the development of secondary neoplasms in childhood cancer survivors, which is illustrated by high-penetrance genetic cancer predisposition syndromes (Table 2.1).[24-27] However, germline mutations in known moderate- to high-penetrance cancer susceptibility genes are only found in 8.5% of paediatric and adolescent cancer patients.[28] Data from the Swedish general population suggest less pathogenic low-penetrance familial cancer predisposition might be more important in the development of malignancies than high-penetrance genetic cancer susceptibility genes.[29] This is illustrated by Friedman et al., who observed an increased cancer risk in siblings of childhood cancer survivors in comparison to the general population (SIR 1.5 [95% CI 1.3-1.7]), even after exclusion of families with suspected high-penetrance genetic cancer predisposition syndromes (SIR 1.3 [95% CI 1.2-1.5]).[30] In their study, siblings and offspring of childhood cancer survivors who developed a secondary malignant neoplasm were even at higher risk of developing cancer in comparison to relatives of childhood cancer survivors who did not develop a secondary malignancy (SIR 2.4 [95% CI 1.5-3.7] for siblings; SIR 15.0 [95% CI 5.3-42.9] for offspring).[30]

Childhood cancer survivors at highest risk for secondary malignant neoplasms include survivors of Hodgkin lymphoma, leukaemia, sarcoma, and central nervous system malignancies (Figure 2.1B).[13, 15, 22] This seems to be related to administered treatment modalities. Radiotherapy is the most important risk factor for the development of secondary neoplasms.[13, 15, 22] Risk for radiation-induced secondary malignant neoplasms depends on cumulative radiation dose, radiotherapy fractionation, radiation field, radiosensitivity, radiotherapy technique, quality of radiation, and other confounding factors.[31] Besides radiotherapy, chemotherapeutic agents (i.e. alkylators, anthracyclines, and topoisomerase II inhibitors), as well as hematopoietic stem cell transplantation have been associated with an increased risk for secondary malignant neoplasms in childhood cancer survivors.[16, 32, 33]

Besides the factors mentioned above, environmental and lifestyle determinants may also be important in secondary tumour development.[34-36] However, studies specifically addressing the risk-modifying effects of these determinants in childhood cancer survivors have to be performed yet.

**Figure 2.1.** Distribution of secondary malignant neoplasms and primary cancer diagnoses among childhood cancer survivors who developed a secondary neoplasm as observed in the Childhood Cancer Survivor Study by Friedman et al.[13]
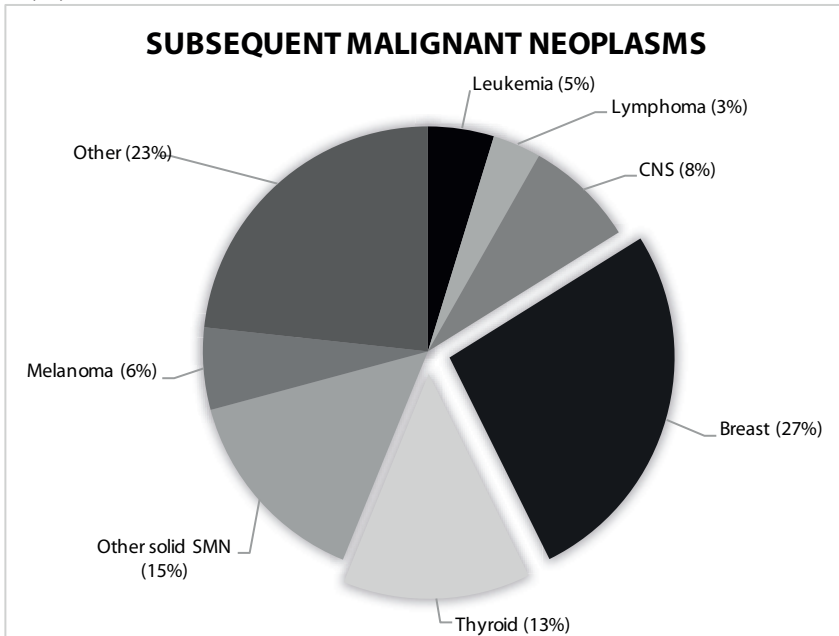


**A:** Secondary malignant neoplasms (non-melanoma skin cancers excluded).
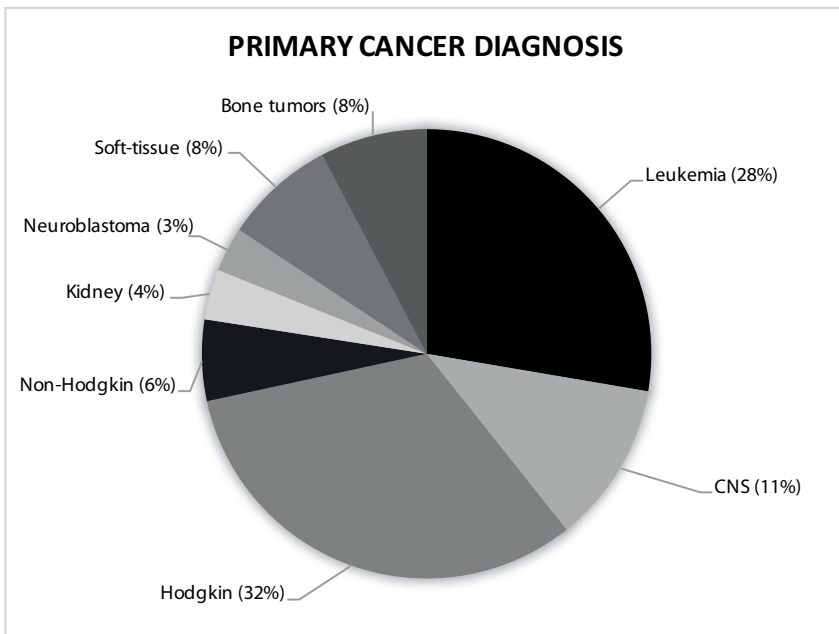


**B:** Primary cancer diagnoses. CNS = central nervous system; SMN = secondary malignant neoplasm.

**Table 2.1.** High-penetrance genetic cancer predisposition syndromes associated with endocrine-related malignancies

| Name | Genes | Associated cancers | References |
|---|---|---|---|
| Hereditary Breast and Ovarian Cancer Syndrome | BRCA1 BRCA2 | Breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, biliary cancer, melanoma | Shiovitz et al.[27] |
| Cowden syndrome (also known as multiple hamartoma syndrome) | PTEN | Breast cancer, non-medullary thyroid cancer, endometrial cancer, genitourinary tumours | Pilarski et al.[24] Shiovitz et al.[27] |
| Li-Fraumeni syndrome (LFS) | TP53 | Breast cancer, sarcoma, brain tumour, adrenocortical tumour, leukaemia, lung cancer | Shiovitz et al.[27] |
| Hereditary Diffuse Gastric Cancer | CDH1 | Breast cancer, gastric cancer, colorectal cancer | Shiovitz et al.[27] |
| Peutz-Jeghers syndrome | STK11 | Gastro-intestinal cancer, breast cancer, ovarian cancer, pancreatic cancer | Strahm et al.[25] Shiovitz et al.[27] |
| Multiple Endocrine Neoplasia type 1 (MEN1) | MEN1 | Parathyroid adenoma, pancreatic endocrine tumours, pituitary adenoma | Pilarski et al.[24] Strahm et al.[25] |
| Multiple Endocrine Neoplasia type 2 (MEN2) | RET | Medullary thyroid carcinoma, pheochromocytoma, parathyroid hyperplasia | Pilarski et al.[24] Strahm et al.[25] |
| Succinate Dehydrogenase complex (SDHX) | SDHB SDHC SDHD | Paraganglioma, pheochromocytoma | Pilarski et al.[24] |
| Von-Hippel Lindau syndrome (VHL) | VHL | Retinal and central nervous system hemangioblastoma, renal cell carcinoma, pheochromocytoma, pancreatic islet cell tumour, endolymphatic sac tumour | Pilarski et al.[24] |
| Adenomatous polyposis of the colon | APC | Colon cancer, small intestine cancer, thyroid cancer, stomach cancer, hepatoblastoma | Strahm et al.[25] |
| Beckwith-Wiedemann syndrome | CDKN1C/ NSD1 | Nephroblastoma, hepatoblastoma, adrenal carcinoma, rhabdomyosarcoma | Strahm et al.[25] |
| DICER1 syndrome | DICER1 | Pleuropulmonary blastoma, ovarian tumour, cystic nephroma, sarcoma, thyroid tumour, pituitary tumour | Foulkes et al.[26] |

## BREAST CANCER

### Epidemiology and host-related risk factors

Breast cancer risk in childhood cancer survivors has recently been addressed in several large cohort studies (Table 2.2).[13-15, 22] After 30 years of follow-up since childhood cancer diagnosis, secondary breast cancer affects approximately 5% of childhood cancer survivors.[13] This represents a standardized incidence ratio of 2.2-9.8 in comparison to the general population.[13-15, 22] Latency periods for the development of secondary breast cancer following childhood cancer vary between 6.7 and 39 years (average 21.8 years) (Table 2.3).[13, 37-45] This is illustrated by Reulen et al., who observed an increased risk for secondary breast cancer in female childhood cancer survivors during the first three decades following primary cancer diagnosis, which gradually declined to general population norms at an attained survivor's age of 50 years.[46]

**Table 2.2.** Risk of secondary breast cancer following childhood cancer in recent large cohort studies

| Study | Year | Study population | Treatment era | Patients | Age at primary cancer Dx (yr.) | Median FU (yr.) | Breast cancer cases | SIR (95% CI) | EAR per 10 000/ yr. (95% CI) | Cumulative incidence at 30 yr. following primary cancer Dx (95% CI) | Median latency time (range) (yr.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Inskip et al.[22] | 2007 | Population-based cohort from United States | 1973-2002 | ♂ 11922 ♀ 14043 | < 18 | 6.3 | 51 | 8.4 | 1.9 | NA | NA |
| Olsen et al.[14] | 2009 | Population-based cohort from Denmark, Finland, Iceland, Norway, and Sweden | 1943-2005 | ♂ 26168 ♀ 21529 | < 20 | NA | 148 | 2.4 (2.0-2.8) | NA | NA | NA |
| Friedman et al.[13] | 2010 | Cohort from 26 institutions in United States and Canada | 1970-1986 | ♂ 7714 ♀ 6645 | < 21 | 22.9 | 252 | 9.8 (8.4-11.5) | NA | 5.0% (4.2-5.9%) | 21.3 (6.7-33.5) |
| Reulen et al.[15] | 2011 | Population-based cohort from Britain | 1940-1991 | ♂/♀ 17981 | < 15 | 24.3 | 97 | 2.2 (1.8-2.7) | 1.4 (0.9-2.0) | NA | NA |

♂ = male; ♀ = female; CI = confidence interval; Dx = diagnosis; EAR = excess absolute risk; FU = follow-up; NA = not available; SIR = standardized incidence ratio; yr. = year.

**Table 2.3.** Latency time between childhood cancer and secondary breast cancer

| Study | Year | Study population | Treatment era | Patients | Age at primary cancer Dx (yr.) | Median follow-up (yr.) | Radiotherapy (%) | Breast cancers (n) | Latency period | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Median (yr.) | Range (yr.) |
| Gold et al.[44] | 2003 | Single-centre cohort of survivors of several childhood cancers from Minnesota | 1954-1980 | ♂/♀ 446 | <18 | 19.5 | 100 | 8 | 20 | 10-32 |
| Taylor et al.[39] | 2007 | Population-based cohort of Hodgkin lymphoma survivors from Britain | 1940-1991 | ♀ 383 | <15 | 20.3[a] | 67.6 | 16 | 21.6[a] | 9.5-34.1 |
| Constine et al.[37] | 2008 | Cohort Hodgkin lymphoma survivors from 5 institutions in the United States | 1960-1990 | ♂ 532 ♀ 398 | <19 | 16.8[a] | 91.2 | 29 | 17.2 | 9.4-36.1 |
| Taylor et al.[38] | 2008 | Population-based cohort of nephroblastoma survivors from Britain | 1940-1991 | ♂ 732 ♀ 709 | <15 | 19.3[a] | 82.4 | 9 | 26.7[a] | 12.4-34.5 |
| Diallo et al.[45] | 2009 | Cohort of survivors of several childhood cancers from 8 institutions in France and Britain | 1942-1986 | ♂/♀ 4581 | <17 | 15.4 | NA | 13 | 21 | 9-37 |
| Friedman et al.[13] | 2010 | Cohort of survivors of several childhood cancers from 26 institutions in United States and Canada | 1970-1986 | ♂ 7714 ♀ 6645 | <21 | 22.9 | 68.0 | 252 | 21.3 | 6.7-33.5 |
| O'Brien et al.[41] | 2010 | Single-centre cohort of Hodgkin lymphoma survivors from Stanford | 1970-1990 | ♂ 75 ♀ 35 | <19 | 20.6 | 100 | 6 | 16.6 | 12.1-29.9 |
| Lange et al.[43] | 2014 | Cohort of nephroblastoma survivors from the National Wilms Tumour Studies 1-4 | 1969-1995 | ♀ 2492 | <20 | NA | 50.7 | 28 | 27.1 | 7.9-35.7 |
| Dorffel et al.[40] | 2015 | Cohort from German, Austrian, and Swiss paediatric Hodgkin lymphoma studies | 1978-2002 | ♂ 1424 ♀ 1124 | <19 | 14.3 | NA | 37 | 22.0 | 14.3-32.1 |
| Henderson et al.[42] | 2015 | Cohort of survivors of several childhood cancers from 26 institutions in United States and Canada | 1970-1986 | ♀ 3768 | <21 | 25.5 | 0 | 47 | 24.0 | 10.0-34.0 |

[a]Mean. ♂ = male; ♀ = female; Dx = diagnosis; n = number; NA = not available; yr. = year.

Several studies identified pubertal age at primary cancer diagnosis to be an important risk factor for secondary breast cancer.[37, 47, 48] In a study by Metayer et al., risk for secondary breast cancer was highest in women aged 10-16 years at Hodgkin lymphoma diagnosis.[47] In addition, 114 of the 120 secondary breast cancers observed in a study by Inskip et al. were diagnosed in women aged 10-20 years at childhood cancer diagnosis.[48] Therefore, an increased susceptibility of proliferating breast tissue for carcinogenic factors in adolescent girls has been suggested.[47-49] However, several other studies could not confirm a risk-modifying effect of age at childhood cancer diagnosis.[46, 50, 51] This inconsistency might be explained by shorter follow-up durations since childhood cancer in studies reporting an increased secondary breast cancer risk by pubertal age compared to studies not reporting such an effect (average 11.0-16.8 vs. 16-25.1 years).[37, 46, 47, 50] Secondary breast cancer risk in childhood cancer survivors by follow-up since childhood cancer diagnosis, attained survivor's age, and at age at childhood cancer diagnosis is represented in Table 2.4.[22, 46, 50, 52]

Genetic susceptibility might contribute to secondary breast cancer development in childhood cancer survivors. This is illustrated by studies reporting an increased secondary breast cancer risk in survivors of childhood cancer with a positive family history for breast and/or ovarian cancer.[52, 53] However, germline mutations in known high- to moderate-penetrance breast cancer susceptibility genes like *BRCA1*, *BRCA2*, *TP53*, and *ATM* are only found in a minority of childhood cancer survivors who develop a secondary breast malignancy.[54, 55] Therefore, less pathogenic low-penetrance genetic susceptibility might be more important. Recent studies identified allelic variants in *PRDM1* and *FGFR2* to predispose Hodgkin lymphoma survivors to radiation-induced breast cancer.[56, 57]

Noteworthy, Kenney et al. identified presence of thyroid disease to be a risk factor for secondary breast cancer in childhood cancer survivors (RR 1.7 [95% CI 1.1-2.6]).[52] An association between thyroid disease and breast cancer has also been observed in the general population.[58, 59] Although no clear explanations for this finding have been found, stimulation of breast cancer cells by deregulated thyroid hormone receptors, oestrogen-receptor activation by triiodothyronine, and a potential role of the sodium-iodide symporter expressed in breast cancer tissue have been proposed.[60-62]

**Treatment-related risk factors for secondary breast cancer**

*Radiotherapy*

Chest irradiation is the most important treatment-related risk factor for secondary breast cancer in childhood cancer survivors. In a recent review, Henderson et al. summarized the risk for secondary breast cancer after treatment with chest irradiation for paediatric cancer.[63] In the included higher-quality cohort studies, standardized incidence ratios for secondary breast cancer varied between 13.3-55.5, excess absolute risks between 18.6-79.0 per 10 000 person-years, and cumulative incidences between 12-26% at 25-30 years

follow-up since childhood cancer.[37, 39, 52, 64-66] These risk estimates are comparable to risks for breast cancer in women harbouring a germline *BRCA1* or *BRCA2* gene mutation.[67]

Radiation fields associated with an increased secondary breast cancer risk in childhood cancer survivors include mantle field, whole lung, hemithorax, mediastinum, supra-diaphragmatic abdomen, axilla, neck and clavicle, as well as total body (Table 2.5).[43, 66-68] Smaller radiation fields seem to be associated with lower risks for radiation-induced breast cancer.[21, 66, 68] However, despite an increased use of less-extensive supradiaphragmatic radiation fields over the past decades, the incidence of radiation-induced breast cancer remained stable in Hodgkin lymphoma survivors.[21] This may be partly related to an earlier detection of secondary breast malignancies by improved screening practices.[69] In a recent study on secondary breast cancer risk after craniospinal irradiation for paediatric central nervous system malignancies and leukaemia, Moskowitz et al. observed an increased risk for secondary breast cancer in the subgroup of leukaemia survivors solely (SIR 3.8 [95% CI 1.2-11.7]).[70] This observation might be related to genetic susceptibility, as illustrated by a population-based study in Italy that observed an increased standardized mortality ratio attributable to breast cancer in mothers of children diagnosed with leukaemia.[71]

The relationship between chest radiation dose and breast cancer risk has been inves-tigated by several studies (Table 2.6).[48, 50, 51, 53, 72] A linear dose-response curve has been established (Figure 2.2A).[48, 73] Risk for radiation-induced breast cancer was traditionally studied after moderate- to high-dosed chest irradiation (i.e. ≥ 20 Gy).[63] However, recent studies also demonstrated an increased secondary breast cancer risk after lower-dosed chest irradiation.[43, 67] Lange et al. observed an increased breast cancer risk of 14.4% (95% CI 7.6-30.1) at an attained survivors' age of 40 years after 1-12 Gy chest irradiation for nephroblastoma.[43] In a recent study by Moskowitz et al., breast cancer risk was 30.6-fold increased (95% CI 18.4-50.7) in comparison to the United States general population after 10-19 Gy chest irradiation for various childhood cancer subtypes.[67] Currently, there is no evidence of a significant effect of radiotherapy fractionation on secondary breast cancer risk following childhood cancer.[50]

Studies investigating radiation-related secondary cancer risk in childhood cancer survivors have predominantly assessed older radiotherapeutic modalities.[31] Contem-porary radiotherapeutic techniques like conformal radiotherapy, intensity-modulated radiation therapy, and proton-beam therapy allow for more precise radiation delivery to the tumour target, thereby sparing healthy surrounding tissue. Therefore, these tech-niques may yield lower risks for secondary malignant neoplasm development compared to older radiotherapeutic modalities of earlier treatment eras.[31, 74] However, there are also concerns of a potentially increased secondary cancer risk following modern radio-therapeutic techniques due to a larger amount of leakage radiation.[31] To our knowledge, observational studies on secondary breast cancer risk in childhood cancer survivors following modern radiotherapeutic techniques have to be performed yet.

**Table 2.4.** Secondary breast cancer risk in childhood cancer survivors by follow-up since primary cancer diagnosis, attained survivors' age, and age at primary cancer diagnosis

| Study | Year | Study population | Treatment era | Patients | Follow-up (yr.) | Breast cancers (n) | | Follow-up since Dx (SIR [95% CI]) | Follow-up since Dx (EAR per 10 000 per year [95% CI]) |
|---|---|---|---|---|---|---|---|---|---|
| Kenney et al.[52] | 2004 | Cohort from 26 institutions in United States and Canada | 1970-1986 | ♀ 6068 | Median 18.5 | 111 | 5-9 yr. | 6.3 (2.0-20.3) | NA |
| | | | | | | | 10-14 yr. | 11.8 (7.0-19.8) | |
| | | | | | | | 15-19 yr. | 9.2 (5.8-14.5) | |
| | | | | | | | ≥ 20 yr. | 6.0 (3.8-9.4) | |
| Guibout et al.[50] | 2005 | Cohort of solid tumour survivors from 8 institutions in France and Britain | 1946-1986 | ♀ 1814 | Mean 16 | 16 | NA | NA | NA |
| Inskip et al.[22] | 2007 | Population-based cohort from United States | 1973-2002 | ♂ 11922 ♀ 14043 | Median 6.3 | 51 | 0.16-< 1 yr. | 0 | NA |
| | | | | | | | 1-4 yr. | 0 | |
| | | | | | | | 5-9 yr. | 7.6 | |
| | | | | | | | 10-14 yr. | 15.1 | |
| | | | | | | | 15-19 yr. | 11.8 | |
| | | | | | | | ≥ 20 yr. | 5.0 | |
| Reulen et al.[46] | 2008 | Population-based cohort from Britain | 1940-1991 | ♀ 8093 | Mean 25.1 | 81 | 5-9 yr. | 9.3 (1.3-66.3) | 0.2 (0.0-2.0) |
| | | | | | | | 10-19 yr. | 9.2 (6.1-14.0) | 1.9 (1.8-4.7) |
| | | | | | | | 20-29 yr. | 2.6 (1.8-3.8) | 4.2 (2.2-8.0) |
| | | | | | | | 30-39 yr. | 1.5 (1.0-2.3) | 4.9 (1.4-17.0) |
| | | | | | | | ≥ 40 yr. | 1.0 (0.5-1.8) | 0.0 |

| Study | Attained age (SIR [95% CI]) | | Attained age (EAR per 10 000 per year [95% CI]) | Age at Dx (SIR [95% CI]) | | Age at Dx (EAR per 10 000 per year [95% CI]) |
|---|---|---|---|---|---|---|
| Kenney et al.[52] | NA | NA | NA | 0-20 yr. | 24.7 (19.3-31.0) | NA |
| Guibout et al.[50] | 3-9 yr. | 0 | NA | 0-16 yr. | 16.9 (9.9-26.6) | NA |
| | 10-19 yr. | 185.0 (30.8-572.6) | | | | |
| | 20-29 yr. | 18.8 (4.7-48.9) | | | | |
| | 30-39 yr. | 23.2 (11.6-40.6) | | | | |
| | ≥ 40 yr. | 2.9 (0.2-12.8) | | | | |
| Inskip et al.[22] | NA | NA | NA | 0-17 yr. | 8.4 | 1.9 |
| Reulen et al.[46] | 0-19 yr. | 10.9 (1.5-77.0) | 0.1 (0.0-1.2) | 0-4 yr. | 2.5 (1.7-3.6) | 1.7 (0.8-3.6) |
| | 20-29 yr. | 5.7 (3.3-9.8) | 1.9 (1.0-3.7) | 5-9 yr. | 1.1 (0.6-2.1) | 0.0 |
| | 30-39 yr. | 3.1 (2.3-4.3) | 8.5 (5.3-13.6) | 10-14 yr. | 2.5 (1.9-3.4) | 5.8 (3.5-9.7) |
| | 40-49 yr. | 1.5 (1.0-2.3) | 6.9 (2.0-23.7) | | | |
| | ≥ 50 yr. | 0.9 (0.5-1.8) | 0.0 | | | |

♀ = female; CI = confidence interval; Dx = diagnosis; EAR = excess absolute risk; *n* = number; NA = not available; SIR = standardized incidence ratio; yr. = year.

**Table 2.5.** Secondary breast cancer risk after various radiation fields

| Study | Year | Study population | Treatment era | Patients | Age at primary cancer Dx (yr.) | Breast cancers (n) | Radiation field | Median radiation dose in Gy (range) | SIR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| De Bruin et al.[66] | 2009 | Cohort of Hodgkin lymphoma survivors from 5 institutions in the Netherlands | 1965-1995 | ♀ 1122 | < 51 (27.7% < 21 yr.) | 120 | Mantle | NA | 8.2 (6.6-10.1) |
| | | | | | | | Mediastinal | | 3.7 (1.2-8.7) |
| | | | | | | | Other supradiaphragmatic | | 1.6 (0.3-4.6) |
| | | | | | | | Infradiaphragmatic | | 0.0 |
| Swerdlow et al.[68] | 2012 | Population-based cohort of England and Wales | 1956-2003 | ♀ 5002 | < 36 (23.7% < 20 yr.) | 373 | Mantle | 36 | 6.0 (5.3-6.7) |
| | | | | | | | Two mantle component fields[a] | 31-33 | 3.4 (2.4-4.7) |
| | | | | | | | One mantle component field[a] | 31-33 | 2.5 (1.7-3.7) |
| Lange et al.[43] | 2014 | Cohort of nephroblastoma survivors from the National Wilms Tumour Studies 1-4 | 1969-1995 | ♀ 2492 | < 20 | 28 | Chest | NA | 27.6 (16.1-44.2) |
| | | | | | | | Abdominal | | 6.0 (2.9-11.0) |
| Moskowitz et al.[67] | 2014 | Cohort of survivors of several childhood cancers from 26 institutions in United States and Canada | 1970-1986 | ♀ 1230 | < 21 | 203 | Mantle | 40 (5-54) | 24.2 (20.7-28.3) |
| | | | | | | | Mediastinal | 30 (3-54) | 13.0 (8.4-20.2) |
| | | | | | | | Whole lung | 14 (2-20) | 43.6 (27.1-70.1) |
| | | | | | | | Total body | 12 (4-16) | 19.3 (7.3-51.5) |
| | | | | | | | Abdominal[b] | 20 (4-40) | 10.8 (2.7-43.2) |
| | | | | | | | Posterior chest[c] | 31 (6-54) | 0.0 |
| | | | | | | | Other one-sided anterior | 41 (10-61) | 9.9 (3.2-30.6) |

[a] Mediastinum, axilla, neck or clavicle. [b] Abdominal field extending above diaphragm. [c] Posterior thoracic or paravertebral fields. ♂ = male; ♀ = female; CI = confidence interval; Dx = diagnosis; Gy = Gray; n = number; NA = not available; SIR = standardized incidence ratio; yr. = year.

**Table 2.6.** Estimated excess relative risk for secondary breast cancer per Gy chest irradiation in childhood cancer survivors

| Study | Year | Study population | Treatment era | Patients[a] | Age at primary cancer Dx (yr.) | ERR for subsequent breast cancer per Gy (95% CI) |
|---|---|---|---|---|---|---|
| Travis et al.[51] | 2003 | Nested case-control study in a cohort of Hodgkin lymphoma survivors from 6 population-based cohorts | 1965-1994 | Cases 105 Controls 266 | < 31 | 0.15 (0.04-0.73) |
| Van Leeuwen et al.[72] | 2003 | Nested case-control study in a cohort of Hodgkin lymphoma survivors from 4 institutions in the Netherlands | 1965-1988 | Cases 48 Controls 175 | < 41 | 0.03 (0.002-0.06) |
| Guibout et al.[50] | 2005 | Cohort of solid tumour survivors from 8 institutions in France and Britain | 1946-1986 | 1814 | < 17 | 0.13 (< 0.00-0.75) |
| Hill et al.[53] | 2005 | Nested case-control study in 6 population-based cohorts of Hodgkin lymphoma survivors | 1965-1999 | Cases 105 Controls 266 | < 31 | 1.04 (1.00-1.07)[b] |
| Inskip et al.[48] | 2009 | Nested case-control study in a cohort of survivors of several childhood cancers from 26 institutions in United States and Canada | 1970-1986 | Cases 120 Controls 464 | < 21 | 0.36 (0.14-0.93) |

[a] All patients were females. [b] Relative risk per Gy. CI = confidence interval; Dx = diagnosis; ERR = excess relative risk; yr. = year.

**Figure 2.2.** Fitted radiation dose-response relationships for chest irradiation and breast cancer, as well as thyroid gland irradiation and thyroid cancer as observed as in the Childhood Cancer Survivors Study by Inskip et al.[48] and Bhatti et al.[102], respectively
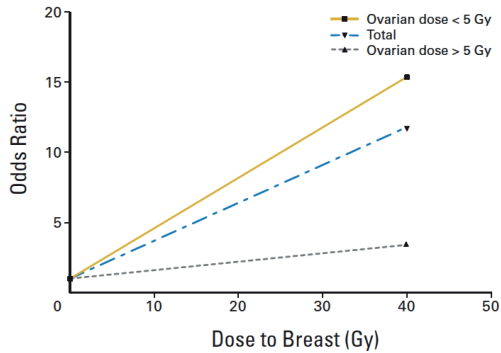


**A:** Fitted dose-response relationship between chest radiation and breast cancer risk by radiation dose to the chest and ovaries. Reprinted with kind permission from Inskip et al. J Clin Oncol 27(24), 2009: 3901-7. © 2009 American Society of Clinical Oncology. All rights reserved.
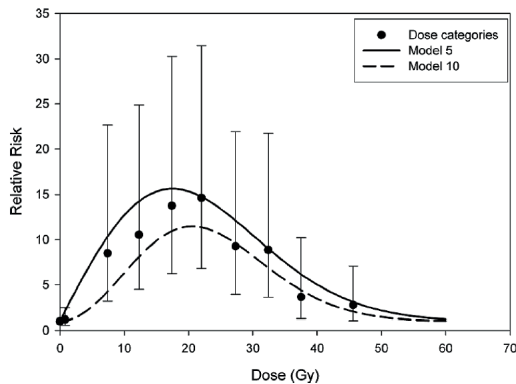


**B:** Fitted dose-response relationship for thyroid gland irradiation and thyroid cancer risk (based on two constructed models [model 5 and 10] and adjusted for attained age, gender, and primary childhood cancer subtype).[102] Reprinted with kind permission from Bhatti et al. Radiat Res 174(6), 2010: 741-752. © 2010 Radiation Research Society. All rights reserved.

*Hematopoietic stem cell transplantation*

Childhood cancer survivors who received hematopoietic stem cell transplantation are at increased risk for secondary breast cancer.[75, 76] Friedman et al. observed a standardized incidence ratio of 2.2 (95% CI 1.7-2.9) for secondary breast cancer following allogeneic hematopoietic stem cell transplantation. In their study, secondary breast cancer risk was associated with total body irradiation, follow-up duration, and age at stem cell transplantation.[76] In addition, Danner-Koptik et al. observed a standardized incidence ratio of 93 (95% CI 11-336) for secondary breast cancer following autologous hematopoietic stem cell transplantation. However, they could not demonstrate an association between

secondary breast cancer risk and age, gender, childhood cancer subtype, follow-up duration, response to primary cancer treatment, and use of total body irradiation or etoposide as part of pretransplant conditioning regimen.[75] Intriguingly, three cases of secondary breast cancer in male childhood cancer survivors following total body irradiation and hematopoietic stem cell transplantation have been described.[77-79]

*Chemotherapy*
Although most studies in cohorts of childhood cancer survivors solely and childhood- and adult-onset cancer survivors combined did not observe a relationship between chemotherapy and secondary breast cancer risk,[46, 50, 80, 81] or observed a protective effect of certain chemotherapeutic agents on the development of radiation-related breast cancer,[21, 51, 66, 68, 72, 82] two studies reported an increased risk for secondary breast cancer attributable to chemotherapy.[42, 83] In a combined cohort of childhood- and adult-onset Hodgkin lymphoma survivors, Hancock et al. observed a higher risk for secondary breast cancer following treatment with mechlorethamine, vincristine, pro- carbazine, and prednisone in combination with radiotherapy compared to treatment with radiotherapy alone during the first fifteen years following Hodgkin lymphoma (SIR 6.3 [95% CI 3.1-11.6] for combination chemoradiation therapy vs. SIR 0.8 [95% CI 0.1- 2.5] for radiotherapy alone). After fifteen years of follow-up since Hodgkin lymphoma, secondary breast cancer risk became equivalently increased in both treatment groups (SIR 14.8 [95% CI 3.7-40.4] for combination chemoradiation therapy vs. SIR 13.0 [95% CI 6.6-23.1] for radiotherapy alone).[83] In addition, in a recent Childhood Cancer Survivor Study report by Henderson et al. on the risk for secondary breast cancer in childhood cancer survivors not treated with chest irradiation, exposure to anthracyclines and al- kylating agents was associated with an increased secondary breast cancer risk (relative SIR 3.8 [95% CI 1.7-8.3] for anthracyclines dosed $\geq 250$ mg/m$^2$, and relative SIR 3.0 [95% CI 1.2-7.7] for alkylating agents dosed $\geq 18\,000$ mg/m$^2$ compared to no treatment with anthracyclines or alkylating agents).[42] As suggested by Van Leeuwen et al., the observed increased risk for secondary breast cancer attributable to anthracyclines and alkylating agents in childhood cancer survivors not treated with chest irradiation might be partly related to genetic susceptibility.[84]

**Primary cancer diagnosis and secondary breast cancer risk**
In a series of three articles, Maule et al. reported standardized incidence ratios and excess absolute risks for secondary malignant neoplasms in childhood cancer survivors derived from thirteen population-based cancer registries.[85-87] They observed an increased risk for secondary breast cancer after several childhood cancer subtypes (Table 2.7). The high- est risk for secondary breast cancer was observed in survivors of Hodgkin lymphoma,[87] which likely reflect treatment with mantle field irradiation. However, Guibout et al. also

observed an increased risk for secondary breast cancer in Hodgkin lymphoma survivors after adjustment for chest irradiation and treatment with chemotherapy (RR 7.01 [95% CI 1.4-30.9] compared to survivors of other childhood cancer subtypes).[50] This supports the idea that factors other than treatment exposures, like genetic determinants, may also contribute to secondary breast cancer development in Hodgkin lymphoma survivors. Although Maule et al. did not observe a significantly increased risk for secondary breast cancer in survivors of soft-tissue sarcoma, retinoblastoma, nephroblastoma, neuroblastoma, germ cell tumours, and non-Hodgkin lymphoma, other studies did.[15, 22, 43, 50, 52, 81, 88] The increased risk for secondary breast cancer in survivors of sarcoma might also be partly related to genetic factors. Data from the Childhood Cancer Survivor Study demonstrated an increased standardized incidence ratio for secondary breast cancer in sarcoma survivors not treated with chest irradiation (5.3 [95% CI 3.6-7.8]).[42] In addition, a positive family history for sarcoma was associated with an increased secondary breast cancer risk (RR 5.3 [95% CI 1.3-21.5]).[52] The increased risk for secondary breast cancer after retinoblastoma is observed in both heritable and non-heritable retinoblastoma survivors,[81] and seems to become apparent after ≥ 40 years of follow-up since primary cancer diagnosis in heritable retinoblastoma survivors.[88]

**Table 2.7.** Risk for secondary breast cancer by childhood cancer subtype[85-87]

| Primary childhood cancer diagnosis | SIR (95% CI) | EAR per 100 000 person-years |
|---|---|---|
| Leukaemia | 2.42 (0.06-13.5) | 0.8 |
| Hodgkin lymphoma | 20.9 (7.66-45.4) | 40.6 |
| Non-Hodgkin lymphoma | 0.00 (0.00-0.33) | -1.7 |
| Glioma | 1.4 (0.2-5.2) | 1.3 |
| Other central nervous system tumours | 1.3 (0.0-7.4) | 2.5 |
| Retinoblastoma | 1.5 (< 0.1-8.5) | 1.6 |
| Renal tumours | 3.0 (0.1-16.7) | 2.7 |
| Bone sarcomas | 6.8 (1.9-17.5) | 26.9 |
| Soft-tissue sarcomas | 1.3 (< 0.1-7.4) | 1.1 |
| Epithelial tumours | 1.8 (0.5-4.6) | 8.7 |

CI = confidence interval; EAR = excess absolute risk; SIR = standardized incidence ratio.

### Hormonal influences on secondary breast cancer risk

In the general population, prolonged exposure to oestrogens has been associated with an increased breast cancer risk.[89] Therefore, several studies investigated the risk-modifying effects of age at menarche, menopausal age, and age at first childbirth on secondary breast cancer in childhood- and young adult-onset cancer survivors.[51-53, 66, 72, 90] In contrast to observations in the general population, Cooke et al. demonstrated an increased risk for secondary breast cancer in Hodgkin lymphoma survivors experiencing

a late menarche (OR 3.74 [95% CI 1.08-12.98] for age at menarche 17 vs. 13 years).[90] In addition, they observed a relationship between timing of chest irradiation in relation to menarche and secondary breast cancer risk. Secondary breast cancer risk was significantly increased in survivors treated with chest irradiation within five years of menarche; the smaller the interval between chest irradiation and menarche, the higher the risk for secondary breast cancer ($P < 0.001$ for trend).[90] Other studies could not demonstrate an association between age at menarche and secondary breast cancer risk.[52, 53, 72] In addition, no studies observed a risk-modifying effect of age at first childbirth on secondary breast cancer development in childhood- and young adult-onset cancer survivors.[52, 53, 72] However, Hill et al. demonstrated a relationship between timing of childbirth in relation to Hodgkin lymphoma diagnosis and secondary breast cancer risk. Women not treated with alkylating agents or ovarian irradiation ≥ 5 Gy who had childbirth within five years following Hodgkin lymphoma diagnosis demonstrated an increased secondary breast cancer risk compared to women who had childbirth at least five years after Hodgkin lymphoma diagnosis (OR 2.6 [95% CI 1.0-6.7]).[53] An increased risk for breast cancer shortly after childbirth has also been observed in the general population, and is thought to be related to gestational hormone exposure, immunosuppressive effects of pregnancy, and postpartum breast involution.[91]

Several studies investigated the risk-modifying effects of age at menopause, premature ovarian insufficiency, alkylating agents, and ovarian irradiation on radiation-induced breast cancer in survivors of childhood- and young adult-onset cancer (Table 2.8).[21, 39, 51-53, 66, 72, 90] Studies in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors consistently reported a protective effect of premature ovarian insufficiency on radiation-induced breast cancer risk.[51, 53, 66, 72, 90] Risk for radiation-induced breast cancer seems to be lower in women experiencing less premenopausal years following Hodgkin lymphoma treatment.[66, 90] Alkylating agent chemotherapy and ovarian irradiation are known to potentially induce premature ovarian insufficiency. Therefore, several studies investigated the risk-modifying effects of these therapies on radiation-induced breast cancer development. A protective effect of alkylating agent chemotherapy on radiation-induced breast cancer has been observed in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors.[21, 51, 66, 68, 72, 82] In the studies by Travis et al. and Van Leeuwen et al., increasing cycles of alkylating agent chemotherapy and a high dose of procarbazine were significantly associated with a decreased risk for radiation-induced breast cancer.[51, 72] Noteworthy, no studies in cohorts of childhood cancer survivors solely could demonstrate a beneficial effect of alkylating agents on radiation-induced breast cancer risk. In addition, several studies in cohorts of childhood cancer survivors solely and childhood- and adult-onset cancer survivors combined observed a protective effect of ovarian irradiation on radiation-induced breast cancer (Figure 2.2A).[37, 48, 52, 67, 68]

**Table 2.8.** Risk-modifying effects of gonadotoxic treatment, premature ovarian insufficiency, and age at menopause on secondary breast cancer risk in childhood cancer survivors

| Study | Year | Study population | Treatment era | Patients | Age at primary cancer Dx (yr.) | RR (95% CI) associated with alkylating agents (yes vs. no) | RR (95% CI) associated with ovarian irradiation (yes vs. no) | RR (95% CI) associated with premature ovarian insufficiency (yes vs. no)[h] |
|---|---|---|---|---|---|---|---|---|
| **Studies in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors** | | | | | | | | |
| Travis et al.[51] | 2003 | Nested case-control study in a cohort of Hodgkin lymphoma survivors from 6 population-based cohorts | 1965-1994 | Cases 105 Controls 266 | < 31 | 0.7 (0.3-1.7) 1-4 cycles<br>0.6 (0.3-1.1) 5-8 cycles<br>0.2 (0.1-0.7) ≥ 9 cycles | 0.4 (0.1-1.1)[g] | 0.2 (0.05-0.6) < 30 yr.<br>0.3 (0.1-0.8) 30-39 yr. |
| Van Leeuwen et al.[72] | 2003 | Nested case-control study in a cohort of Hodgkin lymphoma survivors from 4 institutions in the Netherlands | 1965-1988 | Cases 48 Controls 175 | < 41 | 0.31 (0.09-1.05) < 6 cycles<br>0.33 (0.13-0.86) ≥ 6 cycles | 0.13 (0.02-1.08)[g] | 0.09 (0.01-0.81) 19-30 yr.<br>0.25 (0.07-0.92) 31-40 yr.<br>0.84 (0.23-3.05) ≥ 41 yr. |
| Hill et al.[53] | 2005 | Nested case-control study in 6 population-based cohorts of Hodgkin lymphoma survivors | 1965-1999 | Cases 105 Controls 266 | < 31 | NA | NA | 0.3 (0.2-0.7)[i] |
| De Bruin et al.[66a] | 2009 | Cohort of Hodgkin lymphoma survivors from 5 institutions in the Netherlands | 1965-1995 | ♀ 1122 | < 51 (27.7% < 21 yr.) | 0.6 (0.3-0.9)[b,c]<br>0.4 (0.1-1.3)[b,d] | 0.4 (0.1-1.4)[b] | 0.4 (0.2-0.8)[b] |

**Table 2.8.** Risk-modifying effects of gonadotoxic treatment, premature ovarian insufficiency, and age at menopause on secondary breast cancer risk in childhood cancer survivors (continued)

| Study | Year | Study population | Treatment era | Patients | Age at primary cancer Dx (yr.) | RR (95% CI) associated with alkylating agents (yes vs. no) | RR (95% CI) associated with ovarian irradiation (yes vs. no) | RR (95% CI) associated with premature ovarian insufficiency (yes vs. no)[h] |
|---|---|---|---|---|---|---|---|---|
| Cooke et al.[90] | 2013 | Nested case-control study in a cohort of Hodgkin lymphoma survivors from Wales and Britain treated with chest irradiation | 1956-2003 | Cases 260 Controls 2237 | < 36 | NA | NA | 0.65 (0.44-0.94)[i] |
| Schaapveld et al.[21] | 2015 | Cohort of Hodgkin lymphoma survivors from 7 institutions in the Netherlands | 1965-2000 | ♂ 2207 ♀ 1698 | 15-50 | 0.84 (0.52-1.36)[b,e] 0.71 (0.47-1.07)[b,f] 0.33 (0.16-0.68)[b,g] | NA | NA |
| **Studies in cohorts childhood cancer survivors solely** | | | | | | | | |
| Kenney et al.[52] | 2004 | Cohort from 26 institutions in United States and Canada | 1970-1986 | ♀ 6068 | < 21 | 0.8 (0.4-1.6) AA-score 1-2 0.8 (0.4-1.4) AA-score 3-4 1.11 (0.6-2.0) AA-score ≥ 5 | 0.6 (0.4-0.9) | NA |
| Taylor et al.[39] | 2007 | Population-based cohort of Hodgkin lymphoma survivors from Britain | 1940-1991 | ♀ 383 | < 15 | 0.49 (0.18-1.33) | NA | NA |

[a] Analyses of risk-modifying effects restricted to women < 41 years of age at Hodgkin lymphoma diagnosis. [b] Hazard ratio. [c] $\leq$ 8.4 g/m$^2$ procarbazine. [d] > 8.4 g/m$^2$ procarbazine. [e] $\leq$ 4.2 g/m$^2$ procarbazine. [f] 4.2-8.4 g/m$^2$ procarbazine. [g] $\geq$ 5 Gy ovarian irradiation. [h] Premature ovarian insufficiency is defined as menopause < 40 years of age. [i] Odds ratio. ♂ = male; ♀ = female; AA-score = alkylating agent score (i.e. a categorical variable accounting for exposure to various alkylating agents and a range of doses developed by Tucker et al. [129]); CI = confidence interval; Dx = diagnosis; Gy = Gray; NA = not available; RR = relative risk; yr. = years.

Although the aforementioned studies suggest protective effects of premature ovarian insufficiency and gonadotoxic therapies on radiation-induced breast cancer development, it is important to keep in mind that most of these studies were performed in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors.[21, 51, 53, 66, 68, 72, 82, 90] The beneficial effects of gonadotoxic treatment on radiation-induced breast cancer risk seem less pronounced in childhood- compared to adult-onset cancer survivors. This is underscored by a recent study in survivors of Hodgkin lymphoma by Swerdlow et al., which observed a beneficial effect of gonadotoxic therapy on radiation-induced breast cancer risk only in women aged ≥ 20 years at primary cancer treatment.[68] The less pronounced protective effect of gonadotoxic therapy in childhood- compared to adult-onset cancer survivors may be explained by a greater reserve of follicles in young women, which might be less likely to deplete following ovarian toxic treatment.[92] Noteworthy, in a recent study in childhood cancer survivors not treated with chest irradiation, Henderson et al. could not demonstrate a protective effect of ovarian irradiation or alkylating agent chemotherapy on secondary breast cancer risk.[42] This indicates gonadotoxic treatment only protects for radiation-induced breast cancer development.

Currently, there is no evidence of a harmful effect of oestrogen-progestin replacement therapy on secondary breast cancer risk in premature ovarian insufficient childhood cancer survivors.[51, 66, 72] However, the number of women using oestrogen-progestin replacement therapy in the available studies addressing this issue is too small to reliably evaluate this topic. Only recently, oestrogen-progestin replacement therapy is prescribed commonly in premature ovarian insufficient childhood cancer survivors.[72] Since potential benefits of premature ovarian insufficiency on radiation-induced breast cancer risk have not been demonstrated in cohorts of childhood cancer survivors solely, and harms of oestrogen-progestin replacement therapy on radiation-induced breast cancer risk in premature ovarian insufficient childhood cancer survivors have not been described thus far, castration of female childhood cancer survivors at high risk for radiation-induced breast cancer should not be performed. This is underscored by the clearly demonstrated beneficial effects of oestrogen-progestin replacement therapy on bone and cardiovascular health, as well as quality of life in women from the general population experiencing premature ovarian insufficiency.[93] The effect of oral contraceptives on secondary breast cancer risk in childhood cancer survivors has only been studied in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors. No risk-modifying effects have been demonstrated.[53, 66, 72]

## THYROID CANCER

### Epidemiology and host-related risk factors

Several recent large cohort studies in childhood cancer survivors observed significantly increased standardized incidence ratios for secondary thyroid carcinoma between 5.4-18.0 in comparison to the general population.[13, 14, 22, 94] This represents a 30-year cumulative incidence of 1.4% (95% CI 1.1-1.6) since childhood cancer diagnosis.[13] The increased risk for secondary thyroid cancer in childhood cancer survivors involves predominantly differentiated thyroid carcinoma (i.e. papillary or follicular thyroid carcinoma).[94, 95] Latency periods for the development of secondary thyroid carcinoma in childhood cancer survivors vary between 0.6-38 years (average 12.3 years) (Table 2.9).[37, 40, 45, 75, 94-101] In a recent study by Veiga et al., which included pooled data from the Childhood Cancer Survivor Study cohort,[102] the Late Effects Study Group cohort,[103] the Nordic countries cohort,[104] and a combined French and British cohort,[105] female gender (RR 2.0 [95% CI 1.5-2.8]), younger age at primary cancer (*P* < 0.01 for trend), longer follow-up since primary cancer (*P* = 0.01 for trend), older attained survivor's age (*P* < 0.01 for trend), and treatment with radiotherapy (RR 5.5 [95% CI 3.1-9.7]) were significantly associated with secondary thyroid carcinoma risk in childhood cancer survivors.[106] A risk-modifying effect of gender and age at childhood cancer diagnosis has also been observed in other studies,[37, 98] but not all.[94, 107] A recent study by De Vathaire et al. investigated the influence of smoking and overweight on secondary thyroid cancer risk in childhood cancer survivors, but could not demonstrate a significant effect (RR 0.75 [95% CI 0.32-1.6] for smoking; RR 1.4 [95% CI 0.7-2.80 for overweight]).[108] Best et al. identified allelic variants in *PRDM1* to predispose Hodgkin lymphoma survivors to radiation-induced thyroid cancer.[56] In addition, several studies identified allelic variants in *TP53*, *ATM*, and *FOXE1* to be associated with radiation-induced papillary thyroid carcinoma in survivors of the Chernobyl nuclear accident.[109-111]

### Treatment-related risk factors for secondary thyroid carcinoma

Radiotherapy involving the thyroid gland is the most important risk factor for secondary thyroid carcinoma in childhood cancer survivors, and seems to exert its effect via a sigmoidal dose-response relationship.[106, 108] In the aforementioned pooled study by Veiga et al., the dose-response relationship for thyroid carcinoma in survivors of paediatric cancer increased linearly until a radiation dose of approximately 10 Gy, levelled off at a radiation dose of approximately 10-30 Gy, and declined again at a radiation dose > 30 Gy. However, the risk for thyroid cancer still remained increased at a radiation dose > 50 Gy.[106] The downturn in the dose-response relationship for radiation-induced thyroid carcinoma is thought to be related to a cell-killing effect.[112] In Figure 2.2B, the dose-response curve for secondary thyroid carcinoma following thyroid gland irradiation as

**Table 2.9.** Latency time between childhood cancer and secondary thyroid cancer

| Study | Year | Study population | Treatment era | Patients | Age at primary cancer Dx (yr.) | Median follow-up (yr.) | Radiotherapy (%) | Thyroid cancers (*n*) | Latency period | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Median (yr.) | Range (yr.) |
| Black et al.[95] | 1998 | Population-based study in Germany, Austria, and Switzerland | 1980–1997 | NA | < 16 | NA | NA | 18 | 8 | 4-19 |
| Bhatia et al.[97] | 2002 | Cohort of leukaemia survivors from 122 institutions in United States and Canada | 1983–1995 | ♂ 5034 ♀ 3797 | < 21 | 15 | 38 | 4 | 9.7 | 5.5-11.8 |
| Acharya et al.[96] | 2003 | Single-centre cohort of survivors of several childhood cancers from the United States | 1970–1998 | ♂ 10 ♀ 23 | < 21 | NA | 100 | 33 | 13.0 | 6.2-30.1 |
| Cohen et al.[98] | 2007 | Cohort of hematopoietic stem cell transplantation survivors from 166 institutions participating in the European Group for Blood and Marrow Transplantation (EBMT) registry | 1985–2003 | ♂ 40148 ♀ 30538 | < 52 (27.5% < 21 yr.) | 12.7 | 75.0 | 32 | 8.5 | 0.6-18.5 |
| Constine et al.[37] | 2008 | Cohort of Hodgkin lymphoma survivors from 5 institutions in the United States | 1960–1990 | ♂ 532 ♀ 398 | < 19 | 16.8[a] | 91.2 | 14 | 14.4 | 8.5-23.0 |
| Diallo et al.[45] | 2009 | Cohort of survivors of several childhood cancers from 8 institutions in France and Britain | 1942–1986 | ♂/♀ 4581 | < 17 | 15.4 | NA | 17 | 18 | 8-38 |

**Table 2.9.** Latency time between childhood cancer and secondary thyroid cancer (continued)

| Study | Year | Study population | Treatment era | Patients | Age at primary cancer Dx (yr.) | Median follow-up (yr.) | Radiotherapy (%) | Thyroid cancers (n) | Latency period | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Median (yr.) | Range (yr.) |
| Taylor et al.[94] | 2009 | Population-based cohort from Britain | 1940-1991 | ♂/♀ 17980 | < 15 | 17.4 | NA | 50 | 19.5 | 6-38 |
| Veiga et al.[100] | 2012 | Cohort from 26 institutions in United States and Canada | 1970-1986 | ♂ 6621 ♀ 5926 | < 21 | 16[a] | 68.0 | 119 | 14.3[a] | 5-34 |
| Danner-Koptik et al.[75] | 2013 | Cohort of survivors of autologous hematopoietic stem cell transplantation survivors from > 450 institutions participating in the Centre for International Blood and Marrow Transplantation (CIBMT) | 1987-2003 | ♂ 895 ♀ 592 | < 21 | 8 | 22[b] | 5 | 6.8 | 1.9-12.5 |
| Dorffel et al.[40] | 2015 | Cohort from German, Austrian, and Swiss paediatric Hodgkin lymphoma studies | 1978-2002 | ♂ 1424 ♀ 1124 | < 19 | 14.3 | NA | 47 | 13.2 | 4.0-29.2 |
| Finke et al.[101] | 2015 | Population-based cohort from German Childhood Cancer Registry | 1980-2002 | ♂/♀ 33809 | < 15 | NA | NA | 17 | 9.3 | 4.0-17.6 |
| Brignardello et al.[99] | 2016 | Single-centre cohort of survivors of several childhood cancers from Italy | 1985-2007 | ♂ 113 ♀ 84 | < 18 | 15.19 | 100 | 14 | 13.08 | 8.22-23.65 |

[a]Mean. [b]Radiotherapy as part of conditioning regimen for hematopoietic stem cell transplantation. ♂ = male; ♀ = female; Dx = diagnosis; n = number; NA = not available; yr. = year.

reported by Bhatti et al. is shown.[102] This study by Bhatti et al. is also included in the pooled analysis by Veiga et al.[106] Besides increasing the risk for differentiated thyroid carcinoma, radiotherapy involving the thyroid gland is also known to promote the occurrence of benign thyroid nodules in childhood cancer survivors (Table 2.10). Clinically, it may be difficult to distinguish malignant from benign thyroid nodules.[96, 99, 107, 113-120] Studies investigating radiation-related thyroid carcinoma risk after childhood cancer treatment have predominantly assessed older radiotherapeutic modalities. To our knowledge, observational studies on secondary thyroid carcinoma risk in childhood cancer survivors treated with modern radiotherapeutic techniques like conformal radiotherapy, intensity-modulated radiation therapy, and proton-beam therapy have to be performed yet.

A few studies demonstrated an increased risk for secondary thyroid carcinoma in childhood cancer survivors attributable to chemotherapy.[100, 106, 108] Veiga et al. observed a 2.4-fold increased risk (95% CI 1.3-4.5) for secondary thyroid cancer in childhood cancer survivors treated with a combination of alkylating agents and ≤ 20 Gy thyroid gland irradiation; the contribution of chemotherapy to secondary thyroid cancer risk declined with increasing thyroid gland irradiation dose ($P = 0.03$ for trend).[100] In another study, Veiga et al. observed a 4.5-fold increased risk (95% CI 1.4-17.8) for secondary thyroid carcinoma in childhood cancer survivors treated with anthracyclines without thyroid gland irradiation.[106] A recent study by De Vathaire et al. demonstrated an increased secondary thyroid carcinoma risk in childhood cancer survivors treated with nitrosourea chemotherapy (RR 6.6 [95% CI 2.5-15.7]).[108] Interestingly, in this study by De Vathaire et al., childhood cancer treatment with splenectomy was also associated with an increased risk for secondary thyroid cancer (RR 2.3 [95% CI 1.3-4.0]); while pituitary irradiation > 10 Gy decreased secondary thyroid carcinoma risk (RR 0.2 [95% CI 0.1-0.6]).[108] In our institution, we could not demonstrate an increased risk for secondary thyroid cancer in survivors of childhood Hodgkin lymphoma treated with chemotherapy solely.[121, 122]

Autologous and allogeneic hematopoietic stem cell transplantation are also associated with an increased secondary thyroid cancer risk.[75, 98, 118, 123] In a cohort of childhood- and adult-onset autologous and allogeneic hematopoietic stem cell transplantation survivors, Cohen et al. identified young age at transplantation (RR 24.61 [95% CI 4.45-136.25] for age 0-10 vs. > 20 years), pretransplant conditioning with total body irradiation (RR 3.44 [95% CI 1.41-8.37]), and chronic graft-versus-host disease (RR 2.94 [95% CI 1.21-7.15]) to increase the risk for secondary thyroid cancer.[98]

**Primary cancer diagnosis and secondary thyroid carcinoma risk**

Several childhood cancer subtypes have been associated with an increased secondary thyroid cancer risk (Table 2.11). Particularly high risks for secondary thyroid carcinoma have been observed in survivors of neuroblastoma, Hodgkin lymphoma, non-Hodgkin

lymphoma, brain tumours, and leukaemia.[85-87] In addition, De Vathaire et al. observed an increased risk for secondary thyroid carcinoma in survivors of gonadal tumours (SIR 16.0 [95% CI 4.0-41.4]) and soft-tissue sarcoma (SIR 8.2 [95% CI 2.0-21.2]).[108] Administered treatment modalities, like ^{131}I-MIBG (131-iodine metaiodobenzylguanidine) and radiotherapy involving the thyroid gland may conceivably explain the increased risks for secondary thyroid cancer. ^{131}I-MIBG may be used to treat neuroblastoma, and involves administering a radioiodine-labelled guanidine derivate.[124] Approximately 2-5% of the administered ^{131}I-MIBG enters the circulation as free radioiodine, and may affect thyroid functioning and induce thyroid nodules as well as secondary thyroid carcinoma.[125]

## LIMITATIONS OF CURRENTLY AVAILABLE LITERATURE, AND RECOMMENDATIONS FOR FUTURE RESEARCH

The currently available literature on secondary endocrine-related cancer risk in childhood cancer survivors has some limitations. Follow-up durations since childhood cancer are generally too short to assess the risk for secondary malignant neoplasms in aging childhood cancer survivors. Average follow-up durations since childhood cancer vary between 6.3-27.3 years in studies assessing secondary breast cancer risk,[15, 21, 22, 37, 40, 44, 47, 50, 64-66, 70, 75, 76, 80, 81, 83, 85, 88, 90] and 5.1-27 years in studies investigating secondary thyroid carcinoma risk.[13, 22, 37, 40, 75, 85, 94, 97-99, 108, 114, 116, 118, 119, 121, 126] Specific subtypes of secondary malignant neoplasms and potential risk-modifying factors yet unknown may become apparent at an advanced survivor's age. Therefore, it is important to prospectively evaluate the growing cohort of aging childhood cancer survivors.

Furthermore, a large amount of the evidence on secondary breast cancer risk in childhood cancer survivors,[13, 40-42, 48, 52, 67, 70, 88] and to a lesser extent on secondary thyroid cancer risk in childhood cancer survivors,[13, 40, 100, 102, 108, 112] has been derived from retrospective cohort studies using self-reported data to ascertain secondary malignant neoplasms, which may predispose to selection bias. Another source for selection bias may be the nature of the cohort. This is illustrated by Ness et al., who observed an overestimation of the prevalence of long-term adverse health conditions by 9.3% (95% CI 7.0-11.6) in childhood cancer survivors ascertained in a hospital- compared to a population-based setting.[127] Future studies on secondary endocrine-related malignancies after childhood cancer could be prospective, based on national registries, and use objective methods to collect data on secondary malignant neoplasms.

Although several studies reported a protective effect of gonadotoxic therapies and premature ovarian insufficiency on radiation-induced breast cancer,[21, 37, 48, 51-53, 66, 67, 72, 82, 90] it is important to consider that most of these studies were performed in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors.[21, 51, 53, 66, 72, 82, 90] Since

**Table 2.10.** Detection and presence of benign and malignant thyroid nodules in childhood cancer survivors

| Study | Year | Study population | Treatment era | Patients | Age at primary cancer Dx (yr.) | Median follow-up (yr.) | RTx (%) | Method of nodule detection | Benign nodules (%) | Malignant nodules (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Acharya et al.[96] | 2003 | Single-centre cohort of survivors of several childhood cancers from the United States | 1970-1998 | ♂ 10 ♀ 23 | < 21 | NA | 100 | Retrospective search in hospital-based databases for thyroid nodules in childhood cancer survivors and histological confirmation by pathologist | 20 (60.6%) | 13 (39.4%) |
| Agrawal et al.[113] | 2016 | Single-centre cohort of survivors of several childhood cancers from the United States | NA | ♂ 58 ♀ 61 | < 21 | NA | 50.4 | Ultrasonography and histological examination in suspected nodules | 31 (93.9%) | 2 (6.1%) |
| Brignardello et al.[99] | 2016 | Single-centre cohort of survivors of several childhood cancers from Italy | 1985-2007 | ♂ 113 ♀ 84 | < 18 | 15.19 | 100 | Ultrasonography and histological examination in suspected nodules | 60 (81.1%) | 14 (18.9%) |
| Caglar et al.[119] | 2014 | Single-centre cohort of survivors of several childhood cancers from Turkey | NA | ♂ 84 ♀ 36 | < 18 | 7.8[a] | 56.7 | Ultrasonography and histological examination in suspected nodules | 24 (88.9%) | 3 (11.1%) |
| Crom et al.[116] | 1997 | Single-centre cohort of survivors of several childhood cancers from the United States | NA | ♂ 53 ♀ 43 | < 22 | 10.6 | 100 | Ultrasonography and histological examination in suspected nodules | 21 (95.5%) | 1 (4.5%) |
| Haddy et al.[115] | 2012 | Cohort of survivors of several childhood cancers from 5 institutions in France | 1940-1985 | ♂ 1831 ♀ 1423 | < 16 | 25 | 70.3 | Self-reported questionnaire or retrospective search in medical records for histologically confirmed thyroid adenomas | 71 (2.2%) | NA |

**Table 2.10.** Detection and presence of benign and malignant thyroid nodules in childhood cancer survivors (continued)

| Study | Year | Study population | Treatment era | Patients | Age at primary cancer Dx (yr.) | Median follow-up (yr.) | RTx (%) | Method of nodule detection | Benign nodules (%) | Malignant nodules (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Healy et al.[117] | 1996 | Single-centre cohort of Hodgkin lymphoma survivors from Britain | NA | 46 | NA | 10.3 | 100 | Ultrasonography and histological examination in suspected nodules | 28 (93.3%) | 2 (6.7%) |
| Kelly et al.[120] | 2013 | Single-centre cohort of survivors of several childhood cancers from the United States | 1987–2007 | ♂ 17 ♀ 30 | < 18 | 8 | 100 | Ultrasonography and histological examination in suspected nodules | 43 (91.5%) | 4 (8.5%) |
| Li et al.[114] | 2014 | Single-centre cohort of survivors of several childhood cancers from Canada | NA | ♂ 44 ♀ 34 | < 19 | 17.90 | 100 | Retrospective search in medical records for childhood cancer survivors who received ultrasonography and histological examination for suspected nodules | 41 (89.1%) | 5 (10.9%) |
| Somerville et al.[107] | 2002 | Single-centre cohort of survivors of several childhood cancers from Australia | NA | ♂ 72 ♀ 70 | NA | 14.0[a] | 100 | Ultrasonography and histological examination in suspected nodules | 81 (81.8%) | 18 (18.2%) |
| Vivanco et al.[118] | 2012 | Single-centre cohort of survivors of several childhood cancers treated with total body irradiation preceding hematopoietic stem cell transplantation from France | 1989–2009 | ♂ 43 ♀ 33 | < 18 | 5.1 | 100 | Ultrasonography and histological examination in suspected nodules | 15 (71.4%) | 6 (28.6%) |

[a] Mean. ♂ = male; ♀ = female; % = percentage; Dx = diagnosis; NA = not available; RTx = radiotherapy; yr. = year.

the beneficial effects of gonadotoxic treatments on radiation-induced breast cancer risk seem to be less pronounced in childhood- compared to adult-onset cancer survivors,[68] and no studies assessed the risk-modifying effect of a diagnosis of premature ovarian insufficiency on radiation-induced breast cancer in childhood cancer survivors solely, more studies should be performed. Future studies may also address the potential harms and benefits of oestrogen-progestin replacement therapy on radiation-induced breast cancer risk in women experiencing childhood cancer treatment-related premature ovarian insufficiency.

Studies on secondary malignant neoplasms after childhood cancer concern predominantly survivors treated with old-fashioned treatment regimens. Although childhood cancer therapy has changed considerably over the past five decades,[1, 31] results described in this review are still highly valuable for those individuals treated in earlier treatment eras. Since the effects of modern radiotherapeutic techniques like conformal radiotherapy, intensity-modulated radiation therapy, and proton-beam therapy on secondary endocrine-related cancer risk remain unknown, future studies should address the potential risks and benefits associated with these contemporary radiotherapeutic modalities. Risks for radiation-induced malignant neoplasms may be greater in small compared to large children due to a more significant contribution of scatter radiation.[128] Currently, no studies on secondary endocrine-related malignancies after childhood cancer accounted for this issue. Future studies may investigate radiation-induced cancer risks by dosimetry according to body size at cancer treatment.

Finally, there is a lack of studies specifically investigating the influence of environmental and lifestyle factors on secondary endocrine-related cancer risk in childhood cancer survivors. Future studies should address these potentially risk-modifying factors.

**Table 2.11.** Risk for secondary thyroid cancer by childhood cancer subtype[85-87]

| Primary childhood cancer diagnosis | SIR (95% CI) | EAR per 100 000 person-years |
|---|---|---|
| Leukaemia | 18.8 (8.60-35.7) | 11.3 |
| Hodgkin lymphoma | 52.5 (24.0-99.6) | 62.7 |
| Non-Hodgkin lymphoma | 40.4 (14.8-88.0) | 31.0 |
| Glioma | 6.8 (1.9-18.0) | 7.2 |
| Embryonal central nervous system tumours | 30 (8.2-77) | 25 |
| Other central nervous system tumours | 7.7 (0.2-43) | 8.8 |
| Sympathetic nervous system tumours | 143.7 (29.6-419.8) | 60.8 |
| Retinoblastoma | 5.3 (0.1-29.6) | 3.8 |
| Renal tumours | 13.9 (2.9-40.5) | 11.1 |
| Bone sarcomas | 10.8 (1.3-38.9) | 14.3 |
| Soft-tissue sarcomas | 4.1 (0.1-22.6) | 3.6 |
| Epithelial tumours | 3.3 (0.1-18.4) | 3.4 |

CI = confidence interval; EAR = excess absolute risk; SIR = standardized incidence ratio.

## CONCLUSION

Secondary malignant neoplasm development in childhood cancer survivors depends on host factors, primary cancer diagnosis, and types and timing of primary cancer treatment. In addition, environmental factors and lifestyle factors may play a contributing role. Radiotherapy is the most important risk factor for secondary breast and thyroid cancer in childhood cancer survivors. Premature ovarian insufficiency may protect against radiation-induced breast cancer. Although evidence is weak, there seems to be no harmful effect of oestrogen-progestin replacement therapy on radiation-induced breast cancer risk in premature ovarian insufficient childhood cancer survivors. Childhood cancer survivors at risk for secondary endocrine-related malignancies should be regularly screened in a risk-based fashion, preferably by endocrinologists in close collaboration with physicians experienced in long-term complications of childhood cancer treatment.

## REFERENCES

1.  Hudson MM, Link MP & Simone JV. Milestones in the curability of pediatric cancers. *J Clin Oncol* 2014 **32** 2391-2397.
2.  Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, Dimitrova N, Jakab Z, Kaatsch P, Lacour B, Mallone S, Marcos-Gragera R, Minicozzi P, Sanchez-Perez MJ, Sant M, Santaquilani M, Stiller C, Tavilla A, Trama A, Visser O, Peris-Bonet R & Group EW. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. *Lancet Oncol* 2014 **15** 35-47.
3.  Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ & Cronin KAe. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015., 2015.
4.  Siegel DA, King J, Tai E, Buchanan N, Ajani UA & Li J. Cancer incidence rates and trends among children and adolescents in the United States, 2001-2009. *Pediatrics* 2014 **134** e945-955.
5.  Steliarova-Foucher E, Stiller C, Kaatsch P, Berrino F, Coebergh JW, Lacour B & Parkin M. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. *Lancet* 2004 **364** 2097-2105.
6.  Hewitt M, Weiner SL & Simone JV. In *Childhood Cancer Survivorship: Improving Care and Quality of Life*. Washington (DC), 2003.
7.  Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W, Robison LL & Childhood Cancer Survivor S. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006 **355** 1572-1582.
8.  Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, Jaspers MW, Koning CC, Oldenburger F, Langeveld NE, Hart AA, Bakker PJ, Caron HN & van Leeuwen FE. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007 **297** 2705-2715.
9.  Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, Green DM, Armstrong GT, Nottage KA, Jones KE, Sklar CA, Srivastava DK & Robison LL. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA* 2013 **309** 2371-2381.
10. Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL & Mertens AC. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol* 2009 **27** 2328-2338.
11. Hjorth L, Haupt R, Skinner R, Grabow D, Byrne J, Karner S, Levitt G, Michel G, van der Pal H, Bardi E, Beck JD, de Vathaire F, Essig S, Frey E, Garwicz S, Hawkins M, Jakab Z, Jankovic M, Kazanowska B, Kepak T, Kremer L, Lackner H, Sugden E, Terenziani M, Zaletel LZ, Kaatsch P & PanCare N. Survivorship after childhood cancer: PanCare: a European Network to promote optimal long-term care. *Eur J Cancer* 2015 **51** 1203-1211.
12. Armstrong GT, Chen Y, Yasui Y, Leisenring W, Gibson TM, Mertens AC, Stovall M, Oeffinger KC, Bhatia S, Krull KR, Nathan PC, Neglia JP, Green DM, Hudson MM & Robison LL. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. *N Engl J Med* 2016.
13. Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL & Neglia JP. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2010 **102** 1083-1095.

14. Olsen JH, Moller T, Anderson H, Langmark F, Sankila R, Tryggvadottir L, Winther JF, Rechnitzer C, Jonmundsson G, Christensen J & Garwicz S. Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. *J Natl Cancer Inst* 2009 **101** 806-813.

15. Reulen RC, Frobisher C, Winter DL, Kelly J, Lancashire ER, Stiller CA, Pritchard-Jones K, Jenkinson HC, Hawkins MM & British Childhood Cancer Survivor Study Steering G. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. *JAMA* 2011 **305** 2311-2319.

16. Choi DK, Helenowski I & Hijiya N. Secondary malignancies in pediatric cancer survivors: perspectives and review of the literature. *Int J Cancer* 2014 **135** 1764-1773.

17. Ng AK, Kenney LB, Gilbert ES & Travis LB. Secondary malignancies across the age spectrum. *Semin Radiat Oncol* 2010 **20** 67-78.

18. Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, Robison LL & Yasui Y. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2008 **100** 1368-1379.

19. Garwicz S, Anderson H, Olsen JH, Winther JF, Sankila R, Langmark F, Tryggvadottir L, Moller TR, Association of the Nordic Cancer R & Nordic Society for Pediatric Hematology O. Late and very late mortality in 5-year survivors of childhood cancer: changing pattern over four decades--experience from the Nordic countries. *Int J Cancer* 2012 **131** 1659-1666.

20. Reulen RC, Winter DL, Frobisher C, Lancashire ER, Stiller CA, Jenney ME, Skinner R, Stevens MC, Hawkins MM & British Childhood Cancer Survivor Study Steering G. Long-term cause-specific mortality among survivors of childhood cancer. *JAMA* 2010 **304** 172-179.

21. Schaapveld M, Aleman BM, van Eggermond AM, Janus CP, Krol AD, van der Maazen RW, Roesink J, Raemaekers JM, de Boer JP, Zijlstra JM, van Imhoff GW, Petersen EJ, Poortmans PM, Beijert M, Lybeert ML, Mulder I, Visser O, Louwman MW, Krul IM, Lugtenburg PJ & van Leeuwen FE. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. *N Engl J Med* 2015 **373** 2499-2511.

22. Inskip PD & Curtis RE. New malignancies following childhood cancer in the United States, 1973-2002. *Int J Cancer* 2007 **121** 2233-2240.

23. Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, Nesbit ME, Packer RJ, Potter JD, Sklar CA, Smith MA, Stovall M, Strong LC, Yasui Y & Zeltzer LK. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol* 2002 **38** 229-239.

24. Pilarski R & Nagy R. Genetic testing by cancer site: endocrine system. *Cancer J* 2012 **18** 364-371.

25. Strahm B & Malkin D. Hereditary cancer predisposition in children: genetic basis and clinical implications. *Int J Cancer* 2006 **119** 2001-2006.

26. Foulkes WD, Priest JR & Duchaine TF. DICER1: mutations, microRNAs and mechanisms. *Nat Rev Cancer* 2014 **14** 662-672.

27. Shiovitz S & Korde LA. Genetics of breast cancer: a topic in evolution. *Ann Oncol* 2015 **26** 1291-1299.

28. Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, Hedges D, Ma X, Zhou X, Yergeau DA, Wilkinson MR, Vadodaria B, Chen X, McGee RB, Hines-Dowell S, Nuccio R, Quinn E, Shurtleff SA, Rusch M, Patel A, Becksfort JB, Wang S, Weaver MS, Ding L, Mardis ER, Wilson RK, Gajjar A, Ellison DW, Pappo AS, Pui CH, Nichols KE & Downing JR. Germline Mutations in Predisposition Genes in Pediatric Cancer. *N Engl J Med* 2015.

29. Frank C, Fallah M, Sundquist J, Hemminki A & Hemminki K. Population Landscape of Familial Cancer. *Sci Rep* 2015 **5** 12891.

30. Friedman DL, Kadan-Lottick NS, Whitton J, Mertens AC, Yasui Y, Liu Y, Meadows AT, Robison LL & Strong LC. Increased risk of cancer among siblings of long-term childhood cancer survivors: a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev* 2005 **14** 1922-1927.

31. Kumar S. Second malignant neoplasms following radiotherapy. *Int J Environ Res Public Health* 2012 **9** 4744-4759.

32. Meadows AT, Friedman DL, Neglia JP, Mertens AC, Donaldson SS, Stovall M, Hammond S, Yasui Y & Inskip PD. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. *J Clin Oncol* 2009 **27** 2356-2362.

33. Socie G, Baker KS & Bhatia S. Subsequent malignant neoplasms after hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2012 **18** S139-150.

34. Carpenter DO & Bushkin-Bedient S. Exposure to chemicals and radiation during childhood and risk for cancer later in life. *J Adolesc Health* 2013 **52** S21-29.

35. Kamiya K, Ozasa K, Akiba S, Niwa O, Kodama K, Takamura N, Zaharieva EK, Kimura Y & Wakeford R. Long-term effects of radiation exposure on health. *Lancet* 2015 **386** 469-478.

36. Travis LB, Gospodarowicz M, Curtis RE, Clarke EA, Andersson M, Glimelius B, Joensuu T, Lynch CF, van Leeuwen FE, Holowaty E, Storm H, Glimelius I, Pukkala E, Stovall M, Fraumeni JF, Jr., Boice JD, Jr. & Gilbert E. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst* 2002 **94** 182-192.

37. Constine LS, Tarbell N, Hudson MM, Schwartz C, Fisher SG, Muhs AG, Basu SK, Kun LE, Ng A, Mauch P, Sandhu A, Culakova E, Lyman G & Mendenhall N. Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. *Int J Radiat Oncol Biol Phys* 2008 **72** 24-33.

38. Taylor AJ, Winter DL, Pritchard-Jones K, Stiller CA, Frobisher C, Lancashire ER, Reulen RC, Hawkins MM & British Childhood Cancer Survivor S. Second primary neoplasms in survivors of Wilms' tumour--a population-based cohort study from the British Childhood Cancer Survivor Study. *Int J Cancer* 2008 **122** 2085-2093.

39. Taylor AJ, Winter DL, Stiller CA, Murphy M & Hawkins MM. Risk of breast cancer in female survivors of childhood Hodgkin's disease in Britain: a population-based study. *Int J Cancer* 2007 **120** 384-391.

40. Dorffel W, Riepenhausenl M, Luders H, Bramswig J & Schellong G. Secondary Malignancies Following Treatment for Hodgkin's Lymphoma in Childhood and Adolescence. *Dtsch Arztebl Int* 2015 **112** 320-327, i.

41. O'Brien MM, Donaldson SS, Balise RR, Whittemore AS & Link MP. Second malignant neoplasms in survivors of pediatric Hodgkin's lymphoma treated with low-dose radiation and chemotherapy. *J Clin Oncol* 2010 **28** 1232-1239.

42. Henderson TO, Moskowitz CS, Chou JF, Bradbury AR, Neglia JP, Dang CT, Onel K, Novetsky Friedman D, Bhatia S, Strong LC, Stovall M, Kenney LB, Barnea D, Lorenzi E, Hammond S, Leisenring WM, Robison LL, Armstrong GT, Diller LR & Oeffinger KC. Breast Cancer Risk in Childhood Cancer Survivors Without a History of Chest Radiotherapy: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol* 2015.

43. Lange JM, Takashima JR, Peterson SM, Kalapurakal JA, Green DM & Breslow NE. Breast cancer in female survivors of Wilms tumor: a report from the national Wilms tumor late effects study. *Cancer* 2014 **120** 3722-3730.

44. Gold DG, Neglia JP & Dusenbery KE. Second neoplasms after megavoltage radiation for pediatric tumors. *Cancer* 2003 **97** 2588-2596.

45. Diallo I, Haddy N, Adjadj E, Samand A, Quiniou E, Chavaudra J, Alziar I, Perret N, Guerin S, Lefko-poulos D & de Vathaire F. Frequency distribution of second solid cancer locations in relation to the irradiated volume among 115 patients treated for childhood cancer. *Int J Radiat Oncol Biol Phys* 2009 **74** 876-883.

46. Reulen RC, Taylor AJ, Winter DL, Stiller CA, Frobisher C, Lancashire ER, McClanahan FM, Sugden EM, Hawkins MM & British Childhood Cancer Survivor Study The British Childhood Cancer Survi-vor Study Steering G. Long-term population-based risks of breast cancer after childhood cancer. *Int J Cancer* 2008 **123** 2156-2163.

47. Metayer C, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, Joensuu T, van Leeuwen FE, van't Veer MB, Curtis RE, Holowaty EJ, Andersson M, Wiklund T, Gospodarowicz M & Travis LB. Second cancers among long-term survivors of Hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol* 2000 **18** 2435-2443.

48. Inskip PD, Robison LL, Stovall M, Smith SA, Hammond S, Mertens AC, Whitton JA, Diller L, Kenney L, Donaldson SS, Meadows AT & Neglia JP. Radiation dose and breast cancer risk in the childhood cancer survivor study. *J Clin Oncol* 2009 **27** 3901-3907.

49. Barcellos-Hoff MH. New biological insights on the link between radiation exposure and breast cancer risk. *J Mammary Gland Biol Neoplasia* 2013 **18** 3-13.

50. Guibout C, Adjadj E, Rubino C, Shamsaldin A, Grimaud E, Hawkins M, Mathieu MC, Oberlin O, Zucker JM, Panis X, Lagrange JL, Daly-Schveitzer N, Chavaudra J & de Vathaire F. Malignant breast tumors after radiotherapy for a first cancer during childhood. *J Clin Oncol* 2005 **23** 197-204.

51. Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Anders-son M, Wiklund T, Lynch CF, Van't Veer MB, Glimelius I, Storm H, Pukkala E, Stovall M, Curtis R, Boice JD, Jr. & Gilbert E. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA* 2003 **290** 465-475.

52. Kenney LB, Yasui Y, Inskip PD, Hammond S, Neglia JP, Mertens AC, Meadows AT, Friedman D, Robison LL & Diller L. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med* 2004 **141** 590-597.

53. Hill DA, Gilbert E, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Anders-son M, Wiklund T, Lynch CF, Van't Veer M, Storm H, Pukkala E, Stovall M, Curtis RE, Allan JM, Boice JD & Travis LB. Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. *Blood* 2005 **106** 3358-3365.

54. Nichols KE, Heath JA, Friedman D, Biegel JA, Ganguly A, Mauch P & Diller L. TP53, BRCA1, and BRCA2 tumor suppressor genes are not commonly mutated in survivors of Hodgkin's disease with second primary neoplasms. *J Clin Oncol* 2003 **21** 4505-4509.

55. Broeks A, Russell NS, Floore AN, Urbanus JH, Dahler EC, van TVMB, Hagenbeek A, Noordijk EM, Crommelin MA, van Leeuwen FE & van TVLJ. Increased risk of breast cancer following irradiation for Hodgkin's disease is not a result of ATM germline mutations. *Int J Radiat Biol* 2000 **76** 693-698.

56. Best T, Li D, Skol AD, Kirchhoff T, Jackson SA, Yasui Y, Bhatia S, Strong LC, Domchek SM, Nathanson KL, Olopade OI, Huang RS, Mack TM, Conti DV, Offit K, Cozen W, Robison LL & Onel K. Variants at 6q21 implicate PRDM1 in the etiology of therapy-induced second malignancies after Hodgkin's lymphoma. *Nat Med* 2011 **17** 941-943.

57. Ma YP, van Leeuwen FE, Cooke R, Broeks A, Enciso-Mora V, Olver B, Lloyd A, Broderick P, Russell NS, Janus C, Ashworth A, Houlston RS & Swerdlow AJ. FGFR2 genotype and risk of radiation-associated breast cancer in Hodgkin lymphoma. *Blood* 2012 **119** 1029-1031.

58. Hardefeldt PJ, Eslick GD & Edirimanne S. Benign thyroid disease is associated with breast cancer: a meta-analysis. *Breast Cancer Res Treat* 2012 **133** 1169-1177.

59.    Prinzi N, Baldini E, Sorrenti S, De Vito C, Tuccilli C, Catania A, Carbotta S, Mocini R, Coccaro C, Nesca A, Bianchini M, De Antoni E, D'Armiento M & Ulisse S. Prevalence of breast cancer in thyroid diseases: results of a cross-sectional study of 3,921 patients. *Breast Cancer Res Treat* 2014 **144** 683-688.

60.    Silva JM, Dominguez G, Gonzalez-Sancho JM, Garcia JM, Silva J, Garcia-Andrade C, Navarro A, Munoz A & Bonilla F. Expression of thyroid hormone receptor/erbA genes is altered in human breast cancer. *Oncogene* 2002 **21** 4307-4316.

61.    Nogueira CR & Brentani MM. Triiodothyronine mimics the effects of estrogen in breast cancer cell lines. *J Steroid Biochem Mol Biol* 1996 **59** 271-279.

62.    Portulano C, Paroder-Belenitsky M & Carrasco N. The Na+/I- symporter (NIS): mechanism and medical impact. *Endocr Rev* 2014 **35** 106-149.

63.    Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP, Diller LR, Constine LS, Smith RA, Mahoney MC, Morris EA, Montgomery LL, Landier W, Smith SM, Robison LL & Oeffinger KC. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. *Ann Intern Med* 2010 **152** 444-455; W144-454.

64.    Bhatia S, Yasui Y, Robison LL, Birch JM, Bogue MK, Diller L, DeLaat C, Fossati-Bellani F, Morgan E, Oberlin O, Reaman G, Ruymann FB, Tersak J, Meadows AT & Late Effects Study G. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol* 2003 **21** 4386-4394.

65.    Ng AK, Bernardo MV, Weller E, Backstrand K, Silver B, Marcus KC, Tarbell NJ, Stevenson MA, Friedberg JW & Mauch PM. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. *Blood* 2002 **100** 1989-1996.

66.    De Bruin ML, Sparidans J, van't Veer MB, Noordijk EM, Louwman MW, Zijlstra JM, van den Berg H, Russell NS, Broeks A, Baaijens MH, Aleman BM & van Leeuwen FE. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. *J Clin Oncol* 2009 **27** 4239-4246.

67.    Moskowitz CS, Chou JF, Wolden SL, Bernstein JL, Malhotra J, Novetsky Friedman D, Mubdi NZ, Leisenring WM, Stovall M, Hammond S, Smith SA, Henderson TO, Boice JD, Hudson MM, Diller LR, Bhatia S, Kenney LB, Neglia JP, Begg CB, Robison LL & Oeffinger KC. Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol* 2014 **32** 2217-2223.

68.    Swerdlow AJ, Cooke R, Bates A, Cunningham D, Falk SJ, Gilson D, Hancock BW, Harris SJ, Horwich A, Hoskin PJ, Linch DC, Lister TA, Lucraft HH, Radford JA, Stevens AM, Syndikus I & Williams MV. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. *J Clin Oncol* 2012 **30** 2745-2752.

69.    Ng AK, Garber JE, Diller LR, Birdwell RL, Feng Y, Neuberg DS, Silver B, Fisher DC, Marcus KJ & Mauch PM. Prospective study of the efficacy of breast magnetic resonance imaging and mammographic screening in survivors of Hodgkin lymphoma. *J Clin Oncol* 2013 **31** 2282-2288.

70.    Moskowitz CS, Malhotra J, Chou JF, Wolden SL, Weathers RE, Stovall M, Armstrong GT, Leisenring WM, Neglia JP, Robison LL & Oeffinger KC. Breast cancer following spinal irradiation for a childhood cancer: A report from the Childhood Cancer Survivor Study. *Radiother Oncol* 2015 **117** 213-216.

71.    Zuccolo L, Pastore G, Pearce N, Mosso ML, Merletti F & Magnani C. Mortality from cancer and other causes in parents of children with cancer: a population-based study in Piedmont, Italy. *Eur J Cancer Prev* 2007 **16** 390-395.

72.    van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, Crommelin MA, Aleman BM, Broeks A, Gospodarowicz M, Travis LB & Russell NS. Roles of radiation dose, chemo-

therapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst* 2003 **95** 971-980.

73. Berrington de Gonzalez A, Gilbert E, Curtis R, Inskip P, Kleinerman R, Morton L, Rajaraman P & Little MP. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. *Int J Radiat Oncol Biol Phys* 2013 **86** 224-233.

74. Armstrong GT, Stovall M & Robison LL. Long-term effects of radiation exposure among adult survivors of childhood cancer: results from the childhood cancer survivor study. *Radiat Res* 2010 **174** 840-850.

75. Danner-Koptik KE, Majhail NS, Brazauskas R, Wang Z, Buchbinder D, Cahn JY, Dilley KJ, Frangoul HA, Gross TG, Hale GA, Hayashi RJ, Hijiya N, Kamble RT, Lazarus HM, Marks DI, Reddy V, Savani BN, Warwick AB, Wingard JR, Wood WA, Sorror ML & Jacobsohn DA. Second malignancies after autologous hematopoietic cell transplantation in children. *Bone Marrow Transplant* 2013 **48** 363-368.

76. Friedman DL, Rovo A, Leisenring W, Locasciulli A, Flowers ME, Tichelli A, Sanders JE, Deeg HJ, Socie G, Fhcrc & Party EB-LEW. Increased risk of breast cancer among survivors of allogeneic hematopoietic cell transplantation: a report from the FHCRC and the EBMT-Late Effect Working Party. *Blood* 2008 **111** 939-944.

77. Latz D, Alfrink M, Nassar N & Beyerle C. Breast cancer in a male patient after treatment of acute lymphoblastic leukemia including total body irradiation and bone marrow transplantation. *Onkologie* 2004 **27** 477-479.

78. Lowe T, Luu T, Shen J, Bhatia S, Shibata S, Stein A & Somlo G. Male breast cancer 15 years after allogeneic hematopoietic cell transplantation including total body irradiation for recurrent acute lymphoblastic leukemia. *Onkologie* 2008 **31** 266-269.

79. O'Flynn EA, Wilson R, Nerurkar A, Johnston SR & Allen SD. Metastatic breast cancer in a young adult man after total-body irradiation for acute lymphoblastic leukemia. *J Clin Oncol* 2011 **29** e607-609.

80. Alm El-Din MA, Hughes KS, Finkelstein DM, Betts KA, Yock TI, Tarbell NJ, Aisenberg AC & Taghian AG. Breast cancer after treatment of Hodgkin's lymphoma: risk factors that really matter. *Int J Radiat Oncol Biol Phys* 2009 **73** 69-74.

81. Little MP, Schaeffer ML, Reulen RC, Abramson DH, Stovall M, Weathers R, de Vathaire F, Diallo I, Seddon JM, Hawkins MM, Tucker MA & Kleinerman RA. Breast cancer risk after radiotherapy for heritable and non-heritable retinoblastoma: a US-UK study. *Br J Cancer* 2014 **110** 2623-2632.

82. Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Pukkala E, Lynch CF, Pee D, Smith SA, Van't Veer MB, Joensuu T, Storm H, Stovall M, Boice JD, Jr., Gilbert E & Gail MH. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst* 2005 **97** 1428-1437.

83. Hancock SL, Tucker MA & Hoppe RT. Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst* 1993 **85** 25-31.

84. van Leeuwen FE & Ronckers CM. Anthracyclines and Alkylating Agents: New Risk Factors for Breast Cancer in Childhood Cancer Survivors? *J Clin Oncol* 2016 **34** 891-894.

85. Maule M, Scelo G, Pastore G, Brennan P, Hemminki K, Olsen JH, Tracey E, Pukkala E, Weiderpass E, Brewster DH, Tamaro S, Chia KS, Pompe-Kirn V, Kliewer EV, Tonita JM, Martos C, Jonasson JG, Merletti F & Boffetta P. Second malignancies after childhood noncentral nervous system solid cancer: Results from 13 cancer registries. *Int J Cancer* 2011 **129** 1940-1952.

86. Maule M, Scelo G, Pastore G, Brennan P, Hemminki K, Pukkala E, Weiderpass E, Olsen JH, Tracey E, McBride ML, Brewster DH, Pompe-Kirn V, Tonita JM, Kliewer EV, Chia KS, Jonasson JG, Martos

C, Magnani C & Boffetta P. Risk of second malignant neoplasms after childhood central nervous system malignant tumours: an international study. *Eur J Cancer* 2008 **44** 830-839.

87.   Maule M, Scelo G, Pastore G, Brennan P, Hemminki K, Tracey E, Sankila R, Weiderpass E, Olsen JH, McBride ML, Brewster DH, Pompe-Kirn V, Kliewer EV, Chia KS, Tonita JM, Martos C, Jonasson JG, Merletti F & Boffetta P. Risk of second malignant neoplasms after childhood leukemia and lymphoma: an international study. *J Natl Cancer Inst* 2007 **99** 790-800.

88.   Marees T, Moll AC, Imhof SM, de Boer MR, Ringens PJ & van Leeuwen FE. Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. *J Natl Cancer Inst* 2008 **100** 1771-1779.

89.   Clemons M & Goss P. Estrogen and the risk of breast cancer. *N Engl J Med* 2001 **344** 276-285.

90.   Cooke R, Jones ME, Cunningham D, Falk SJ, Gilson D, Hancock BW, Harris SJ, Horwich A, Hoskin PJ, Illidge T, Linch DC, Lister TA, Lucraft HH, Radford JA, Stevens AM, Syndikus I, Williams MV, England, Wales Hodgkin Lymphoma Follow-up G & Swerdlow AJ. Breast cancer risk following Hodgkin lymphoma radiotherapy in relation to menstrual and reproductive factors. *Br J Cancer* 2013 **108** 2399-2406.

91.   Lyons TR, Schedin PJ & Borges VF. Pregnancy and breast cancer: when they collide. *J Mammary Gland Biol Neoplasia* 2009 **14** 87-98.

92.   Sklar C. Maintenance of ovarian function and risk of premature menopause related to cancer treatment. *J Natl Cancer Inst Monogr* 2005 25-27.

93.   National Collaborating Centre for Women's and Children's Health. Management of premature ovarian insufficiency. In *Menopause: Full Guideline*. London, 2015.

94.   Taylor AJ, Croft AP, Palace AM, Winter DL, Reulen RC, Stiller CA, Stevens MC & Hawkins MM. Risk of thyroid cancer in survivors of childhood cancer: results from the British Childhood Cancer Survivor Study. *Int J Cancer* 2009 **125** 2400-2405.

95.   Black P, Straaten A & Gutjahr P. Secondary thyroid carcinoma after treatment for childhood cancer. *Med Pediatr Oncol* 1998 **31** 91-95.

96.   Acharya S, Sarafoglou K, LaQuaglia M, Lindsley S, Gerald W, Wollner N, Tan C & Sklar C. Thyroid neoplasms after therapeutic radiation for malignancies during childhood or adolescence. *Cancer* 2003 **97** 2397-2403.

97.   Bhatia S, Sather HN, Pabustan OB, Trigg ME, Gaynon PS & Robison LL. Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukemia after 1983. *Blood* 2002 **99** 4257-4264.

98.   Cohen A, Rovelli A, Merlo DF, van Lint MT, Lanino E, Bresters D, Ceppi M, Bocchini V, Tichelli A & Socie G. Risk for secondary thyroid carcinoma after hematopoietic stem-cell transplantation: an EBMT Late Effects Working Party Study. *J Clin Oncol* 2007 **25** 2449-2454.

99.   Brignardello E, Felicetti F, Castiglione A, Gallo M, Maletta F, Isolato G, Biasin E, Fagioli F, Corrias A & Palestini N. Ultrasound surveillance for radiation-induced thyroid carcinoma in adult survivors of childhood cancer. *Eur J Cancer* 2016 **55** 74-80.

100.  Veiga LH, Bhatti P, Ronckers CM, Sigurdson AJ, Stovall M, Smith SA, Weathers R, Leisenring W, Mertens AC, Hammond S, Neglia JP, Meadows AT, Donaldson SS, Sklar CA, Friedman DL, Robison LL & Inskip PD. Chemotherapy and thyroid cancer risk: a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev* 2012 **21** 92-101.

101.  Finke I, Scholz-Kreisel P, Hennewig U, Blettner M & Spix C. Radiotherapy and subsequent thyroid cancer in German childhood cancer survivors: a nested case-control study. *Radiat Oncol* 2015 **10** 219.

102.    Bhatti P, Veiga LH, Ronckers CM, Sigurdson AJ, Stovall M, Smith SA, Weathers R, Leisenring W, Mertens AC, Hammond S, Friedman DL, Neglia JP, Meadows AT, Donaldson SS, Sklar CA, Robison LL & Inskip PD. Risk of second primary thyroid cancer after radiotherapy for a childhood cancer in a large cohort study: an update from the childhood cancer survivor study. *Radiat Res* 2010 **174** 741-752.

103.    Tucker MA, Jones PH, Boice JD, Jr., Robison LL, Stone BJ, Stovall M, Jenkin RD, Lubin JH, Baum ES, Siegel SE & et al. Therapeutic radiation at a young age is linked to secondary thyroid cancer. The Late Effects Study Group. *Cancer Res* 1991 **51** 2885-2888.

104.    Svahn-Tapper G, Garwicz S, Anderson H, Shamsaldin A, De Vathaire F, Olsen JH, Dollner H, Hertz H, Jonmundsson G, Langmark F, Lanning M, Sankila R, Tulinius H & Moller T. Radiation dose and relapse are predictors for development of second malignant solid tumors after cancer in childhood and adolescence: a population-based case-control study in the five Nordic countries. *Acta Oncol* 2006 **45** 438-448.

105.    de Vathaire F, Hardiman C, Shamsaldin A, Campbell S, Grimaud E, Hawkins M, Raquin M, Oberlin O, Diallo I, Zucker JM, Panis X, Lagrange JL, Daly-Schveitzer N, Lemerle J, Chavaudra J, Schlumberger M & Bonaiti C. Thyroid carcinomas after irradiation for a first cancer during childhood. *Arch Intern Med* 1999 **159** 2713-2719.

106.    Veiga LH, Lubin JH, Anderson H, de Vathaire F, Tucker M, Bhatti P, Schneider A, Johansson R, Inskip P, Kleinerman R, Shore R, Pottern L, Holmberg E, Hawkins MM, Adams MJ, Sadetzki S, Lundell M, Sakata R, Damber L, Neta G & Ron E. A pooled analysis of thyroid cancer incidence following radiotherapy for childhood cancer. *Radiat Res* 2012 **178** 365-376.

107.    Somerville HM, Steinbeck KS, Stevens G, Delbridge LW, Lam AH & Stevens MM. Thyroid neoplasia following irradiation in adolescent and young adult survivors of childhood cancer. *Med J Aust* 2002 **176** 584-587.

108.    de Vathaire F, Haddy N, Allodji RS, Hawkins M, Guibout C, El-Fayech C, Teinturier C, Oberlin O, Pacquement H, Diop F, Kalhouche A, Benadjaoud M, Winter D, Jackson A, Bezin Mai-Quynh G, Benabdennebi A, Llanas D, Veres C, Munzer M, Nguyen TD, Bondiau PY, Berchery D, Laprie A, Deutsch E, Lefkopoulos D, Schlumberger M, Diallo I & Rubino C. Thyroid Radiation Dose and Other Risk Factors of Thyroid Carcinoma Following Childhood Cancer. *J Clin Endocrinol Metab* 2015 **100** 4282-4290.

109.    Takahashi M, Saenko VA, Rogounovitch TI, Kawaguchi T, Drozd VM, Takigawa-Imamura H, Akulevich NM, Ratanajaraya C, Mitsutake N, Takamura N, Danilova LI, Lushchik ML, Demidchik YE, Heath S, Yamada R, Lathrop M, Matsuda F & Yamashita S. The FOXE1 locus is a major genetic determinant for radiation-related thyroid carcinoma in Chernobyl. *Hum Mol Genet* 2010 **19** 2516-2523.

110.    Akulevich NM, Saenko VA, Rogounovitch TI, Drozd VM, Lushnikov EF, Ivanov VK, Mitsutake N, Kominami R & Yamashita S. Polymorphisms of DNA damage response genes in radiation-related and sporadic papillary thyroid carcinoma. *Endocr Relat Cancer* 2009 **16** 491-503.

111.    Damiola F, Byrnes G, Moissonnier M, Pertesi M, Deltour I, Fillon A, Le Calvez-Kelm F, Tenet V, McKay-Chopin S, McKay JD, Malakhova I, Masyakin V, Cardis E, Lesueur F & Kesminiene A. Contribution of ATM and FOXE1 (TTF2) to risk of papillary thyroid carcinoma in Belarusian children exposed to radiation. *Int J Cancer* 2014 **134** 1659-1668.

112.    Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, Berkow RL, Hammond S, Neglia JP, Meadows AT, Sklar CA, Robison LL & Inskip PD. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. *Lancet* 2005 **365** 2014-2023.

113. Agrawal C, Guthrie L, Sturm MS, Stanek J, Martin L, Henwood-Finley M, Aldrink JH, Olshefski R & O'Brien SH. Comparison of Thyroid Nodule Prevalence by Ultrasound in Childhood Cancer Survivors With and Without Thyroid Radiation Exposure. *J Pediatr Hematol Oncol* 2016 **38** 43-48.

114. Li Z, Franklin J, Zelcer S, Sexton T & Husein M. Ultrasound surveillance for thyroid malignancies in survivors of childhood cancer following radiotherapy: a single institutional experience. *Thyroid* 2014 **24** 1796-1805.

115. Haddy N, El-Fayech C, Guibout C, Adjadj E, Thomas-Teinturier C, Oberlin O, Veres C, Pacquement H, Jackson A, Munzer M, N'Guyen TD, Bondiau PY, Berchery D, Laprie A, Bridier A, Lefkopoulos D, Schlumberger M, Rubino C, Diallo I & de Vathaire F. Thyroid adenomas after solid cancer in childhood. *Int J Radiat Oncol Biol Phys* 2012 **84** e209-215.

116. Crom DB, Kaste SC, Tubergen DG, Greenwald CA, Sharp GB & Hudson MM. Ultrasonography for thyroid screening after head and neck irradiation in childhood cancer survivors. *Med Pediatr Oncol* 1997 **28** 15-21.

117. Healy JC, Shafford EA, Reznek RH, Webb JA, Thomas JM, Bomanji JB & Kingston JE. Sonographic abnormalities of the thyroid gland following radiotherapy in survivors of childhood Hodgkin's disease. *Br J Radiol* 1996 **69** 617-623.

118. Vivanco M, Dalle JH, Alberti C, Lescoeur B, Yakouben K, Carel JC, Baruchel A & Leger J. Malignant and benign thyroid nodules after total body irradiation preceding hematopoietic cell transplantation during childhood. *Eur J Endocrinol* 2012 **167** 225-233.

119. Caglar AA, Oguz A, Pinarli FG, Karadeniz C, Okur A, Bideci A, Kocak U & Bora H. Thyroid abnormalities in survivors of childhood cancer. *J Clin Res Pediatr Endocrinol* 2014 **6** 144-151.

120. Kelly C, Rivard L, Salvi S, Hayani A, Hopkins W, O'Brien S, Martin L & Canner J. Surveillance following head, neck, and chest radiotherapy: thyroid ultrasound monitoring for secondary thyroid malignancy. *Pediatr Blood Cancer* 2013 **60** 140-142.

121. van Beek RD, van den Heuvel-Eibrink MM, Hakvoort-Cammel FG, van den Bos C, van der Pal HJ, Krenning EP, de Rijke YB, Pieters R & de Muinck Keizer-Schrama SM. Bone mineral density, growth, and thyroid function in long-term survivors of pediatric Hodgkin's lymphoma treated with chemotherapy only. *J Clin Endocrinol Metab* 2009 **94** 1904-1909.

122. van Dorp W, van Beek RD, Laven JS, Pieters R, de Muinck Keizer-Schrama SM & van den Heuvel-Eibrink MM. Long-term endocrine side effects of childhood Hodgkin's lymphoma treatment: a review. *Hum Reprod Update* 2012 **18** 12-28.

123. Socie G, Curtis RE, Deeg HJ, Sobocinski KA, Filipovich AH, Travis LB, Sullivan KM, Rowlings PA, Kingma DW, Banks PM, Travis WD, Witherspoon RP, Sanders J, Jaffe ES & Horowitz MM. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. *J Clin Oncol* 2000 **18** 348-357.

124. Kayano D & Kinuya S. Iodine-131 metaiodobenzylguanidine therapy for neuroblastoma: reports so far and future perspective. *ScientificWorldJournal* 2015 **2015** 189135.

125. Clement SC, van Eck-Smit BL, van Trotsenburg AS, Kremer LC, Tytgat GA & van Santen HM. Long-term follow-up of the thyroid gland after treatment with 131I-Metaiodobenzylguanidine in children with neuroblastoma: importance of continuous surveillance. *Pediatr Blood Cancer* 2013 **60** 1833-1838.

126. Clement SC, van Rijn RR, van Eck-Smit BL, van Trotsenburg AS, Caron HN, Tytgat GA & van Santen HM. Long-term efficacy of current thyroid prophylaxis and future perspectives on thyroid protection during 131I-metaiodobenzylguanidine treatment in children with neuroblastoma. *Eur J Nucl Med Mol Imaging* 2015 **42** 706-715.

127.   Ness KK, Leisenring W, Goodman P, Kawashima T, Mertens AC, Oeffinger KC, Armstrong GT & Robison LL. Assessment of selection bias in clinic-based populations of childhood cancer survivors: a report from the childhood cancer survivor study. *Pediatr Blood Cancer* 2009 **52** 379-386.
128.   Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. *Int J Radiat Oncol Biol Phys* 2006 **65** 1-7.
129.   Tucker MA, D'Angio GJ, Boice JD, Jr., Strong LC, Li FP, Stovall M, Stone BJ, Green DM, Lombardi F, Newton W & et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med* 1987 **317** 588-593.

# Chapter 3

## Daily life physical activity in long-term survivors of nephroblastoma and neuroblastoma

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## ABSTRACT

The risk of metabolic late effects after childhood cancer, such as obesity, hypertension, and diabetes, can be positively influenced by a healthy lifestyle with sufficient physical activity. Nevertheless, studies on physical activity in adult survivors of childhood cancer are scarce and involve different and often non-validated questionnaires. We used the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH), which was developed and validated to assess daily life physical activity in the Dutch adult population. The aim of the study was to assess daily life physical activity in Dutch adult long-term nephroblastoma and neuroblastoma survivors. Sixty-seven nephroblastoma and 36 neuroblastoma survivors (median age 30 years; range 18-51) and 60 socio-demographically similar healthy control subjects (median age 32 years; range 18-62) were asked to complete the SQUASH during their regular follow-up visit. The adjusted mean physical activity score in male neuroblastoma survivors (mean 7155; $P$=0.004) was significantly lower than in male controls (mean 10574), whereas it was not significantly lower in male nephroblastoma survivors (mean 9122; $P$=0.108). Adjusted means for physical activity scores in females were not different from their controls. In conclusion, male neuroblastoma survivors were identified as performing less daily physical activity.

## INTRODUCTION

Survival of nephroblastoma and neuroblastoma patients has increased significantly during the last few decades. The increased survival is due to better stratification, improvements of treatment strategies, and optimized supportive care. With a mean survival rate of 92% and 55%, respectively, nephroblastoma and neuroblastoma survivors represent a considerable group of childhood cancer survivors.[1, 2]

Late effects that occur in these survivors include pulmonary, musculoskeletal, renal, and cardiac late effects, second malignant neoplasms, and increased risk of cardiovascular diseases.[3-6] Some of these late effects influencing cardiovascular risk, for example hypertension, obesity, dyslipidaemia, and insulin resistance, that is, the metabolic syndrome, might be positively affected by sufficient physical activity.

According to a recent review, most studies reported less physical activity in childhood cancer survivors than in control subjects. In particular, survivors treated with cranial radiotherapy or amputation are less physically active.[7] Limitations of previously performed research on physical activity in childhood cancer survivors are the lack of objective physical activity measures, validated questionnaires, non-cancer comparison groups, and the heterogeneity of studied diagnostic groups.[7]

The Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) was developed by the Dutch National Institute of Public Health and the Environment to assess daily life physical activity in the Dutch adult population.[8] The SQUASH contains questions about commuting activities, exertion at work or school, household activities, and leisure time and sports during an average week. Although this questionnaire is a subjective measure of physical activity, it has an important advantage over other questionnaires as it was validated using an objective measure: a Computer Science and Applications activity monitor.

The objective of this study was to assess daily life physical activity using the SQUASH and to assess compliance to the Dutch physical activity guidelines in adult long-term survivors of nephroblastoma and neuroblastoma, as compared with a non-cancer comparison group.

## MATERIALS AND METHODS

### Participants

All long-term (i.e. ≥5 years after cessation of treatment) adult survivors of childhood nephroblastoma and neuroblastoma, treated between 1961-2004 in the Erasmus MC-Sophia Children's Hospital and routinely visiting the late effects outpatient clinic were invited to participate in this prospective study. A control group, consisting of siblings,

friends, or neighbours, preferably of the same sex and within an age range of five years of the survivor, was cross-sectionally recruited. This control group was designed as a socio-demographically similar comparison population. Informed consent was obtained according to the Helsinki declaration[9] and the study was approved by the local medical ethical committee. Adult survivors of neuroblastoma stage 4S who did not receive any treatment were excluded from this study. During the regular visit of the survivors, history was taken and physical examination, laboratory tests, and imaging studies were performed. The study took place from October 2009 to March 2011.

### Outcome of interest

Information about daily life physical activity was collected with the SQUASH (Appendix A).[8] The SQUASH expresses physical activity as a score. Physical activity score is the sum of activity scores for each question. A higher physical activity score indicates a higher amount of daily physical activity. Questions are prestructured in commuting activities, activities at work or school, household activities, and leisure time activities including sports. The SQUASH consists of three main queries about physical activity: days per week, average time per day, and intensity. Intensity is subdivided in three categories based on Ainsworth's Compendium of Physical Activities.[10] The method of Wendel-Vos et al. was used for allocating intensity scores to reported activities.[8] For determining intensity categories of reported sports, the method of Ainsworth et al. was used.[10] Mean physical activity score using the SQUASH was reported to be 7850 in a study of healthy males and females (mean age 44 years; standard deviation [SD] 6). To assess compliance to the Dutch guidelines for physical activity,[11] the question "How many days a week do you bicycle, garden, exercise, or do odd jobs, for at least 30 minutes?" was added. If subjects answered this question with ≥5 days, they were considered to adhere to the guideline.[11]

### Data Collection

Information on disease and treatment was obtained from our local database and medical records. To assess the influence of relevant confounders, the following data were collected: information regarding smoking status and education level was collected using a self-designed questionnaire. Smoking status was categorized as non-smoker, former smoker, and current smoker. Educational level was defined by the highest level of educational attainment as selected from three categories based on the Dutch educational system. Height was measured to the nearest millimetre using a Harpenden Stadiometer and weight was measured to the nearest 0.1kg on a standard clinical balance. Body mass index (BMI) was calculated as weight (kg)/height ($m^2$). Spinal deformities were determined in survivors by physical examination. N-terminal pro-brain natriuretic peptide (NT-proBNP) was determined as a marker for heart function in both survivors and con-

trol subjects and was measured using a validated, commercially available immunoassay (Elecsys ProBNP; Roche Diagnostics, Indianapolis, IN), using established methodology.[12]

## Statistics

Statistical analyses were performed with SPSS 18.0 (SPSS Inc., Chicago, IL). Mann-Whitney *U*-tests were used to compare physical activity scores, BMI, and NT-proBNP between survivors and control subjects. Adjusted subgroup-comparisons for sex and diagnosis were performed by calculating the estimated marginal means of the factor scores of the clusters, with adjustments for the confounders age, sex, smoking, educational level, NT-proBNP, and BMI. Multiple linear regression analysis was performed to assess the influence of spinal deformities in survivors only. *P*-values of <0.05 (two-tailed) were considered statistically significant.

## RESULTS

### Patients

One hundred three adult long-term (≥5 years after cessation of treatment) survivors of nephroblastoma and 54 adult survivors of neuroblastoma were eligible to participate in this study. Out of 103 nephroblastoma survivors, 28 could not be contacted for participation (six died after having survived at least five years after cessation of treatment, eight refused to attend the clinic, five were lost to follow-up, six emigrated, and three visited another outpatient clinic). Out of 54 neuroblastoma survivors, 12 could not be contacted for participation (three died after having survived for at least five years after cessation of treatment, three refused to attend the clinic, five were lost to follow-up, and one emigrated). In total, 75 survivors of nephroblastoma and 42 survivors of neuroblastoma were contacted for participation. Eight nephroblastoma survivors (two being ill at the time, one lost to follow-up, and five refused to participate) and six neuroblastoma survivors (three were currently pregnant, two being ill at the time, and one refused to participate) did not participate. In total, 103 adult survivors (67 nephroblastoma and 36 neuroblastoma survivors) participated in the current study. In addition, 60 healthy control subjects were included. The main reason for control subjects not to participate was that they had to take a day off work. Ninety-four percent (*n*=97) of the survivors and 83% (*n*=50) of the control subjects answered all the questions of the SQUASH. Median age of nephroblastoma survivors was 30.2 years (range 18.8-50.8), of neuroblastoma survivors 29.6 years (range 20.4-46.2), and of control subjects 32.1 years (range 18.0-61.7). Median age at diagnosis was 2.3 years (range 0.0-12.7) and median follow-up time after cessation of treatment was 26.2 years (range 6.4-48.9) in nephroblastoma survivors and 27.8 years (range 15.0-44.4) in neuroblastoma survivors. Characteristics of the study participants are shown in Table 3.1.

**Table 3.1.** Baseline characteristics

| | Nephroblastoma | Neuroblastoma | Controls |
|---|---|---|---|
| *n* | 67 | 36 | 60 |
| Male/female | 39/28 | 15/21 | 27/33 |
| Age at follow-up (years)[a] | 30.2 (18.8-50.8) | 29.6 (20.4-46.2) | 32.1 (18.0-61.7) |
| Age at diagnosis (years)[a] | 3.3 (0.0-12.7) | 0.8 (0.0-11.7) | NA |
| Follow-up time (years)[a] | 26.2 (6.4-48.9) | 27.8 (15.0-44.4) | NA |
| Stage: | | | |
|    I | 32 | 6 | NA |
|    II | 13 | 17 | NA |
|    III | 11 | 8 | NA |
|    IV | 3 | 2 | NA |
|    V | 1 | 0 | NA |
|    Unknown | 7 | 3 | NA |
| Surgery (*n*) | 67 | 36 | NA |
| Radiotherapy (*n*) | 35 | 12 | NA |
| Cumulative dose (Gy) | 25 (15-40) | 20 (10-30) | NA |
| Chemotherapy (*n*) | 59 | 31 | NA |
| Smoking: | | | |
|    Non-smoking | 44 (65.7%) | 17 (47.2%) | 28 (46.7%) |
|    Former smoker | 8 (11.9%) | 8 (22.2%) | 10 (16.7%) |
|    Current smoker | 15 (22.4%) | 11 (30.6%) | 19 (31.7%) |
|    Missing | 0 (0.0%) | 0 (0.0%) | 3 (5.0%) |
| Educational status: | | | |
|    Low | 4 (6.0%) | 1 (2.8%) | 1 (1.7%) |
|    Intermediate | 31 (46.3%) | 17 (47.2%) | 33 (55.0%) |
|    High | 32 (47.8%) | 18 (50.0%) | 24 (40.0%) |
|    Missing | 0 (0.0%) | 0 (0.0%) | 2 (3.3%) |

[a]Data are expressed as median (range) or *n*. Gy = Gray; *n* = number; NA = not applicable.

## Outcomes

Physical activity scores in nephroblastoma survivors (*n*=67, missing *n*=3) (median 8140; *P*=0.721) were not different from controls (*n*=60, missing *n*=10) (median 8080), whereas neuroblastoma survivors (*n*=36, missing *n*=3) had lower physical activity scores than controls (median 6685; *P*=0.043). Physical activity scores in female survivors of both nephroblastoma (*n*=28, missing *n*=1) (median 8490; *P*=0.205) and neuroblastoma (*n*=21, missing *n*=2) (median 7190; *P*=0.979) were not significantly different from sex-matched controls (*n*=27, missing *n*=5) (median 7200). Physical activity score of male nephroblastoma survivors (*n*=39, missing *n*=2) was not different from controls (*n*=27, missing *n*=5) (median 8040 vs. 9528; *P*=0.442). Male survivors of neuroblastoma (*n*=15, missing *n*=1),

however, reported a significantly lower physical activity score than male control subjects (median 6390 vs. 9528; $P$=0.031) (Table 3.2).

**Table 3.2.** Daily life physical activity scores, body mass index, and NT-proBNP in survivors and controls[a]

| | Control subjects | Nephroblastoma | *P*-value[d] | Neuroblastoma | *P*-value[e] |
|---|---|---|---|---|---|
| Physical activity score | | | | | |
|    Males | 9528 (2835-20640) | 8040 (3450-16310) | 0.442 | 6390 (840-21150) | 0.031 |
|    Females | 7200 (2480-14220) | 8490 (2295-16410) | 0.205 | 7190 (3710-14070) | 0.979 |
|    Missing | 10 (16.7%) | 3 (4.5%) | | 3 (8.3%) | |
| Adherence to Dutch recommendations[b] | | | | | |
|    Males | 19 (57.5%) | 14 (35.9%) | 0.066 | 5 (33.3%) | 0.119 |
|    Females | 12 (44.4%) | 18 (64.3%) | 0.180 | 10 (47.6%) | 0.920 |
|    Missing | 1 (1.7%) | 0 (0.0%) | | 0 (0.0%) | |
| Body mass index (kg/m$^2$) | | | | | |
|    Males | 23.8 (20.1-35.2) | 24.1 (19.1-32.3) | 0.755 | 24.3 (18.8-36.5) | 0.864 |
|    Females | 25.4 (20.3-41.8) | 24.7 (19.4-36.3) | 0.680 | 23.6 (17.5-30.2) | 0.145 |
|    Missing | 1 (1.7%) | 0 (0.0%) | | 0 (0.0%) | |
| NT-proBNP (pmol/L) | 3.4 (0.5-11.4) | 4.3 (0.5-95.6) | 0.185 | 3.9 (0.5-38.0) | 0.351 |
| High NT-proBNP (*n*)[c] | 0 (0.0%) | 10 (15.4%) | 0.002 | 3 (8.6%) | 0.052 |
|    Missing | 3 (5.0%) | 2 (3.0%) | | 1 (2.8%) | |

[a]Data are expressed as median (range) or *n*. [b]At least five days a week at least 30 minutes of activity. [c]Defined as NT-proBNP >13.5pmol/L. [d]Adult nephroblastoma survivors compared with control subjects. [e]Adult neuroblastoma survivors compared with control subjects. *n* = number; NT-proBNP = N-terminal pro B-type natriuretic peptide.

Female nephroblastoma survivors (*n*=28, missing *n*=0) seemed to adhere more often to the physical activity guidelines (at least 30 minutes of activity per day at least 5 days a week) than female controls (*n*=27, missing *n*=1), however, this difference was not significant (64.3% vs. 44.4%, *P*=0.180). Adherence to the guideline was comparable between female neuroblastoma survivors (*n*=21, missing *n*=0) and female controls (47.6% vs. 44.4%, *P*=0.920) (Table 3.2). Male survivors of nephroblastoma (*n*=39, missing *n*=0) (35.9%, *P*=0.066) and male survivors of neuroblastoma (*n*=15, missing *n*=0) (33.3%, *P*=0.119) seemed to adhere less frequently to the guidelines than male controls (*n*=33, missing *n*=0) (57.5%), however, these differences were not significant (Table 3.2). There were no differences in median BMI and NT-proBNP between survivors and control subjects (Table 3.2), however, both nephroblastoma and neuroblastoma survivors more often had high (>13.5pmol/L) NT-proBNP levels (Table 3.2). Spinal deformities were present in 43/92 (42%) of assessed survivors.

After correction for the possible confounding effects of age, sex, educational level, smoking, NT-proBNP, and BMI, the adjusted mean physical activity scores between female

controls (8062), female nephroblastoma survivors (9235), and female neuroblastoma survivors (7898) were not significantly different (Figure 3.1). The adjusted mean physical activity score in male neuroblastoma survivors was significantly lower compared with male controls (mean 7155 vs. 10574; *P*=0.004). The adjusted mean physical activity score in male nephroblastoma survivors also seemed to be lower than in controls; however, this difference was not significant (mean 9122 vs. 10574; *P*=0.108) (Figure 3.2). Physical activity scores in male control subjects were significantly higher compared with female control subjects (*P*=0.015). To assess the influence of spinal deformities on the physical activity score, we performed a multiple linear regression analysis in survivors only, which enabled us to adjust for age, sex, smoking, educational level, NT-proBNP, and BMI. No associations between physical activity score and spinal deformities were found ($\beta$=1219, *P*=0.116).

**Figure 3.1.** Adjusted mean physical activity scores in females
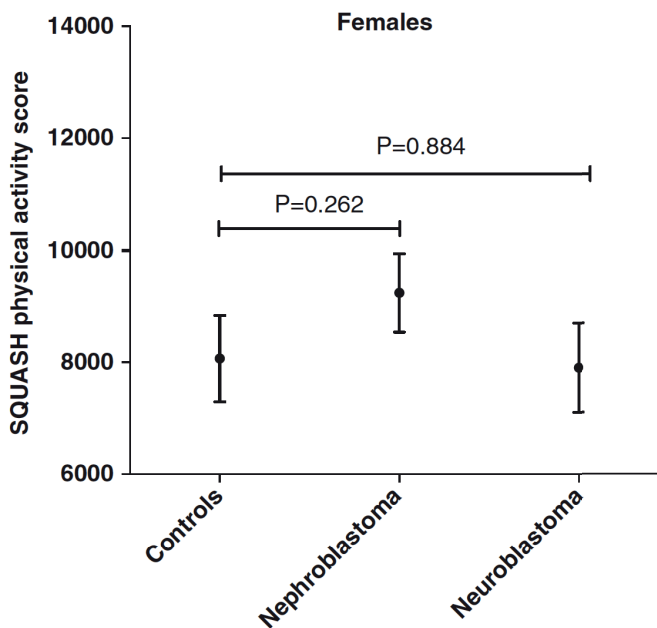


Adjusted means are corrected for age, sex, smoking, educational level, NT-proBNP, and BMI. Female control subjects *n*=33, missing *n*=5. Female nephroblastoma survivors *n*= 28, missing *n*=1. Female neuroblastoma survivors *n*=21, missing *n*=2.

**Figure 3.2.** Adjusted mean physical activity scores in males
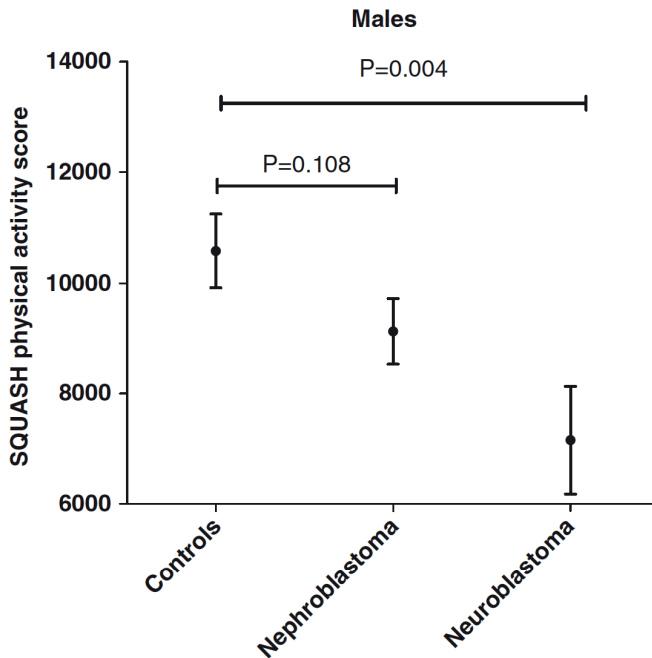


Adjusted means are corrected for age, sex, smoking, educational level, NT-proBNP, and BMI. Male control subjects *n*=27, missing *n*=5. Male nephroblastoma survivors *n*= 39, missing *n*=2. Male neuroblastoma survivors *n*=15, missing *n*= 1.

## DISCUSSION

We investigated daily life physical activity in 67 nephroblastoma and 36 neuroblastoma survivors compared with 60 socio-demographically comparable healthy control subjects. After correction for age, sex, smoking status, educational level, BMI, and NT-proBNP, male survivors of neuroblastoma reported less daily life physical activity than male control subjects.

It is unknown why male neuroblastoma survivors are less physically active than their healthy peers. Specific late effects of cancer treatment could possibly induce such behaviour. Cardiac late effects and deformities such as scoliosis may influence daily life physical activity, but in our study, spinal deformities and NT-proBNP did not influence daily life physical activity.

Physical activity scores in female survivors were not different from female control subjects. It is possible that female survivors are more concerned about their health status and therefore commit more often in physical activity. Compared with the male control subjects, female control subjects were less physically active. This is consistent with previ-

ous reports which showed that healthy males are more physically active than females both on a daily basis and based on committing to sports.[13, 14] Similarly, the percentage of healthy siblings in the Childhood Cancer Survivors Study not meeting the physical activity guidelines was also somewhat higher in females than in males.[15]

Our data concerning male neuroblastoma survivors are in concordance with findings of Ness and colleagues. In contrast to our study, they reported that also female survivors of nephroblastoma and neuroblastoma were more likely to report an inactive lifestyle compared with siblings.[15] Differences in the assessment of not only physical activity but also in health behaviour and lifestyle between the different countries might contribute to these discrepant findings.

Our study has some important strengths. We used a proven reliable and validated questionnaire to assess daily life physical activity, developed specifically for the Dutch adult population. The relatively complete follow-up of survivors limits the possibility of selection bias. Furthermore, we were able to compare physical activity in adult survivors of childhood cancer with an age, sex, and socio-demographically similar control group. Moreover, we investigated the influence of several potential confounders on daily life physical activity. Limitations of our study are the relatively small group of survivors and the use of a subjective measurement of physical activity instead of an objective measurement. Studies in larger groups of survivors might reveal more detailed information on therapy subgroups and their influence on physical activity.

In conclusion, using the SQUASH we found that male neuroblastoma survivors report less daily physical activity than controls. Physical activity in male nephroblastoma survivors and female nephroblastoma and neuroblastoma survivors was comparable with that in controls. Future research on physical activity in adult survivors of childhood cancer should investigate large populations of survivors and focus on all types of childhood malignancies.

### Appendix A: *The short questionnaire to assess health enhancing physical activity (SQUASH)*

Think about an average week in the past months. Please indicate **how many days per week** you performed the following activities, how much time **on average** you were engaged in this, and (if applicable) how strenuous this activity was for you?

| COMMUTING ACTIVITIES (round trip) | days per *week* | average time per *day* | Effort (circle please) |
|---|---|---|---|
| **Walking to/from work or school** | days | hour minutes | slow/moderate/fast |
| **Bicycling to/from work or school** | days | hour minutes | slow/moderate/fast |
| Not applicable | | | |

| LEISURE TIME ACTIVITIES | days per *week* | average time per *day* | Effort (circle please) |
|---|---|---|---|
| **Walking** | days | hour minutes | slow/moderate /fast |
| **Bicycling** | days | hour minutes | slow/moderate /fast |
| **Gardening** | days | hour minutes | light/moderate /intense |
| **Odd jobs** | days | hour minutes | light/moderate /intense |
| **Sports** (please write down yourself) *e.g., tennis, fitness, skating, swimming, dancing* | | | |
| 1. ............................ | days | hour minutes | light/moderate /intense |
| 2. ............................ | days | hour minutes | light/moderate /intense |
| 3. ............................ | days | hour minutes | light/moderate /intense |
| 4. ............................ | days | hour minutes | light/moderate /intense |

| HOUSEHOLD ACTIVITIES | days per *week* | average time per day |
|---|---|---|
| **Light household work** | days | hour minutes |
| (cooking, washing dishes, ironing, child care) | days | hour minutes |
| **Intense household work** (scrubbing floor, walking with heavy shopping bags) | | |

| ACTIVITY AT WORK AND SCHOOL | average time per *week* |
|---|---|
| **Light work** | hour minutes |
| (sitting/standing with some walking, e.g., a desk job) | hour minutes |
| **Intense work** (regularly lifting heavy objects at work) | |
| Not applicable | |

## REFERENCES

1. Bernstein ML, Leclerc JM, Bunin G, Brisson L, Robison L, Shuster J, Byrne T, Gregory D, Hill G, Dougherty G & et al. A population-based study of neuroblastoma incidence, survival, and mortality in North America. *J Clin Oncol* 1992 **10** 323-329.

2. Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL & Bunin GR. Cancer Incidence and Survival among Children and Adolescents: United States. SEER Program 1975-1995, Pub. No. 99-4649. Bethesda, MD: National Cancer Institute, SEER Program. NIH, 1999.

3. van Dijk IW, Oldenburger F, Cardous-Ubbink MC, Geenen MM, Heinen RC, de Kraker J, van Leeuwen FE, van der Pal HJ, Caron HN, Koning CC & Kremer LC. Evaluation of late adverse events in long-term wilms' tumor survivors. *Int J Radiat Oncol Biol Phys* 2010 **78** 370-378.

4. Geenen MM, Bakker PJ, Kremer LC, Kastelein JJ & van Leeuwen FE. Increased prevalence of risk factors for cardiovascular disease in long-term survivors of acute lymphoblastic leukemia and Wilms tumor treated with radiotherapy. *Pediatr Blood Cancer* 2010 **55** 690-697.

5. Laverdiere C, Liu Q, Yasui Y, Nathan PC, Gurney JG, Stovall M, Diller LR, Cheung NK, Wolden S, Robison LL & Sklar CA. Long-term outcomes in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2009 **101** 1131-1140.

6. Wright KD, Green DM & Daw NC. Late effects of treatment for wilms tumor. *Pediatr Hematol Oncol* 2009 **26** 407-413.

7. Stolley MR, Restrepo J & Sharp LK. Diet and physical activity in childhood cancer survivors: a review of the literature. *Ann Behav Med* 2010 **39** 232-249.

8. Wendel-Vos GC, Schuit AJ, Saris WH & Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol* 2003 **56** 1163-1169.

9. World Medical Association (WMA). Declaration of Helsinki - Sixth revision. 2008.

10. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Jr., Montoye HJ, Sallis JF & Paffenbarger RS, Jr. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 1993 **25** 71-80.

11. Kemper HGC, Ooijendijk WTM & Stiggelbout M. [Consensus about the Dutch physical activity guideline]. . *Tijdschrift voor gezondheidswetenschappen* 2000 **3** 180-183.

12. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM & Richards M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J* 2006 **27** 330-337.

13. Aaron DJ, Kriska AM, Dearwater SR, Anderson RL, Olsen TL, Cauley JA & Laporte RE. The epidemiology of leisure physical activity in an adolescent population. *Med Sci Sports Exerc* 1993 **25** 847-853.

14. Fairclough SJ, Boddy LM, Hackett AF & Stratton G. Associations between children's socioeconomic status, weight status, and sex, with screen-based sedentary behaviours and sport participation. *Int J Pediatr Obes* 2009 **4** 299-305.

15. Ness KK, Leisenring WM, Huang S, Hudson MM, Gurney JG, Whelan K, Hobbie WL, Armstrong GT, Robison LL & Oeffinger KC. Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer* 2009 **115** 1984-1994.

# Chapter 4

## Very long-term sequelae of craniopharyngioma

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## ABSTRACT

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

**Design:** Cross-sectional study based on retrospective data.

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

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

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

## INTRODUCTION

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

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

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

## SUBJECTS AND METHODS

### Participants

Patients who were diagnosed with and/or treated for craniopharyngioma at the Erasmus University Medical Centre were eligible for participation in this cross-sectional study based on retrospective data. In order to reduce heterogeneity in our study population

attributable to time-related differences in craniopharyngioma treatment, neuroimaging, and supportive care, we chose to include only patients with craniopharyngioma treated from 1980 onwards. Our local institutional review board approved this study and all patients gave their informed consent.

## Data collection

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

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

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

*Long-term health conditions*

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

*Survival*

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

## Statistics

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 24, Chicago, IL, USA). Continuous variables were described as median and interquartile range; discrete variables as frequencies and percentages. Evaluations were based on the number of patients with available data. Comparisons according to initial craniopharyngioma treatment approach were performed by one-way analyses of variance for continuous variables and Chi-squared tests for discrete variables. In case assumptions were not met, Kruskal-Wallis tests and likelihood ratio statistics were used. Comparisons between patients with childhood- and adult-onset craniopharyngioma were made by Student's *t*-test for continuous variables and Chi-squared tests for discrete variables. Mann-Whitney *U*-tests and likelihood ratio statistics or Fisher's exact tests were used

in case assumptions were not met. Overall and recurrence-/progression-free survival were estimated by Kaplan-Meier methods. Log-rank tests were used to compare survival curves. In case statistical significance was reached in a variable concerning more than two groups, Bonferroni-corrected post-hoc analyses were performed to specify subgroup-related differences. Because certain long-term health conditions may only become apparent after a prolonged follow-up period, and because craniopharyngioma management may have evolved over time due to advances in treatment, neuroimaging, and supportive care, we investigated the influence of treatment decade and follow-up duration since initial craniopharyngioma treatment on the development of long-term health effects using multivariable logistic regression models including treatment decade and follow-up duration as independent variables. We investigated the influence of treatment decade on survival by log-rank tests for trend. A *P*-value < 0.05 (two-tailed) was considered statistically significant.

## RESULTS

### Presenting symptoms

Presenting symptoms in patients with craniopharyngioma are shown in Table 4.1. Visual disturbances, pituitary hormone deficiencies, and headaches were the most common disease manifestations and occurred in 87%, 71%, and 68% of the patients, respectively. Hypogonadotropic hypogonadism was the most common pituitary hormone deficiency and affected 60% of the patients. Diabetes insipidus was found in 7% of the patients. Underweight and obesity affected 10% and 12% of the patients, respectively. Two patients (both with childhood-onset craniopharyngioma) presented with blindness. Patients with childhood-onset craniopharyngioma presented significantly more growth hormone deficiency (53% vs. 27%, *P*<0.01) compared with patients with adult-onset craniopharyngioma. Visual field defects (85% vs. 59%, *P*<0.01), cognitive impairment (16% vs. 3%, *P*=0.02), overweight (39% vs. 16%, *P*<0.01), and secondary hypothyroidism (56% vs. 32%, *P*<0.01) were significantly more common in patients with adult- compared with childhood-onset craniopharyngioma.

### Craniopharyngioma characteristics at diagnosis

Tumour characteristics at diagnosis are depicted in Table 4.1. Tumour consistency was significantly different between patients with childhood- and adult-onset cranio-pharyngioma. Bonferroni-corrected post-hoc analyses revealed a significantly higher number of multicystic craniopharyngiomas in patients with childhood- compared with adult-onset disease (45% vs. 21%; *P*=0.02). Hydrocephalus, as well as hypothalamic and/or third ventricle involvement were also significantly more common in patients with

**Table 4.1.** Baseline characteristics, presenting symptoms, and tumour characteristics at diagnosis

| | All craniopharyngiomas (*n*=128) *n* (%) | Childhood-onset (*n*=63) *n* (%) | Adult-onset (*n*=65) *n* (%) | Childhood - vs. adult-onset *P*-value |
|---|---|---|---|---|
| **Baseline characteristics** | | | | |
| Gender | ♂ 57 (45) | ♂ 25 (40) | ♂ 32 (49) | 0.28 |
| | ♀ 71 (56) | ♀ 38 (60) | ♀ 33 (51) | |
| Median age at presentation (yr.) (interquartile range) | 19 (8-42) | 8 (5-12) | 41 (29-55) | < 0.01 |
| **Presenting symptoms** | | | | |
| Headaches | 83 (68) | 42 (71) | 41 (65) | 0.47 |
| Visual acuity disorders | 73 (73) | 33 (72) | 40 (74) | 0.79 |
| Visual field defects | 72 (74) | 23 (59) | 49 (85) | < 0.01 |
| Epilepsy | 7 (6) | 6 (10) | 1 (2) | 0.06 |
| Neurological deficits | 42 (34) | 25 (42) | 17 (27) | 0.07 |
| Altered level of consciousness | 26 (21) | 15 (25) | 11 (18) | 0.28 |
| Cognitive impairment | 12 (10) | 2 (3) | 10 (16) | 0.02 |
| Behavioural changes | 15 (12) | 8 (14) | 7 (11) | 0.68 |
| History of weight change: | | | | 0.14 |
| -  Increase | 13 (11) | 3 (5) | 10 (16) | |
| -  Decrease | 19 (16) | 9 (15) | 10 (16) | |
| Weight status (BMI [kg/m$^2$]): | | | | |
| -  Underweight (< 18.5) | 10 (10) | 8 (16) | 2 (4) | 0.09 |
| -  Normal weight (18.5-24.9) | 51 (51) | 31 (61) | 20 (41) | 0.05 |
| -  Overweight (25.0-29.9) | 27 (27) | 8 (16) | 19 (39) | < 0.01 |
| -  Class I obesity (30.0-34.9) | 7 (7) | 2 (4) | 5 (10) | 0.26 |
| -  Class II obesity (35.0-39.9) | 2 (2) | 0 (0) | 2 (4) | 0.24 |
| -  Class III obesity (≥ 40.0) | 3 (3) | 2 (4) | 1 (2) | 1.00 |
| -  Class I-III obesity (≥ 30.0) | 12 (12) | 4 (8) | 8 (16) | 0.19 |
| Pituitary hormone deficiencies: | 87 (71) | 40 (68) | 47 (73) | 0.49 |
| -  GH | 48 (40) | 31 (53) | 17 (27) | < 0.01 |
| -  FSH/LH | 49 (60) | 10 (56) | 39 (61) | 0.68 |
| -  ACTH | 42 (34) | 17 (28) | 25 (39) | 0.21 |
| -  TSH | 54 (44) | 19 (32) | 35 (56) | < 0.01 |
| -  ADH | 8 (7) | 4 (7) | 4 (6) | 1.00 |
| -  Anterior PH | 17 (14) | 10 (17) | 7 (12) | 0.39 |
| -  Complete PH | 4 (3) | 2 (3) | 2 (3) | 1.00 |
| **Tumour characteristics** | | | | |
| Localization: | | | | 0.87 |
| -  Intrasellar | 5 (4) | 3 (5) | 2 (3) | |
| -  Suprasellar | 48 (39) | 23 (38) | 25 (40) | |

**Table 4.1.** Baseline characteristics, presenting symptoms, and tumour characteristics at diagnosis (continued)

| | All craniopharyngiomas (*n*=128) *n* (%) | Childhood-onset (*n*=63) *n* (%) | Adult-onset (*n*=65) *n* (%) | Childhood - vs. adult-onset *P*-value |
|---|---|---|---|---|
| - Intra-/suprasellar | 70 (57) | 34 (57) | 36 (57) | |
| Consistency: | | | | 0.02 |
| - Unicystic | 71 (61) | 29 (52) | 42 (69) | |
| - Multicystic | 38 (33) | 25 (45) | 13 (21) | |
| - Solid | 8 (7) | 2 (4) | 6 (10) | |
| Presence of hydrocephalus | 36 (29) | 25 (40) | 11 (18) | < 0.01 |
| Hypothalamic and/or third ventricle involvement | 60 (53) | 35 (66) | 25 (42) | 0.01 |
| Brain stem compression | 16 (14) | 6 (11) | 10 (17) | 0.39 |

Data regarding headaches, epilepsy, neurological deficits, altered level of consciousness, cognitive impairment, behavioural changes, and weight change were missing in six patients. Data regarding visual acuity disorders and visual field defects were missing in 28 and 31 patients, respectively. Weight status could not be determined in 28 patients. Data regarding pituitary hormone deficiencies were missing in eight patients (growth hormone [GH] in seven patients, follicle stimulating hormone/luteinizing hormone [FSH/LH] in four patients, adrenocorticotropic hormone [ACTH] in four patients, thyroid stimulating hormone [TSH] in five patients, antidiuretic hormone [ADH] in four patients, and anterior and complete panhypopituitarism [PH] in eight patients). 42 patients were too young to reliably assess gonadal function (girls < 14 years of age; boys < 15 years of age). Data regarding initial craniopharyngioma localization, consistency, hydrocephalus, hypothalamic and/or third ventricle involvement, and brain stem compression were missing in five, 11, three, 15, and 14 patients, respectively. ♂ = male; ♀ = female; % = percentage; BMI = body mass index; $kg/m^2$ = kilograms per square metre; *n* = number; yr. = years.

childhood- compared with adult-onset craniopharyngioma (40% vs. 18%, *P*<0.01; 66% vs. 42%, *P*=0.01). Patient and tumour characteristics were not significantly different between different initial craniopharyngioma treatment approaches (Table 4.2).

## Craniopharyngioma treatment

In the patients who were initially treated with neurosurgical excision, the neurosurgical approach was transsphenoidal in 35 patients (39%), subfrontal in 31 patients (35%), pterional in 20 patients (23%), transcallosal in two patients (2%), and supra-orbital in one patient (1%). In five patients (5%) data regarding the neurosurgical approach were missing. There were no significant differences in the neurosurgical approaches used between patients treated with gross total resection, subtotal resection without radiotherapy, and subtotal resection with radiotherapy. Initial craniopharyngioma treatment approaches, as well as neurosurgical approaches were not significantly different between patients with childhood- and adult-onset craniopharyngioma. In the patients who initially received radiotherapy, conventional external beam radiotherapy was applied to eight patients and stereotactic radiotherapy to 16 patients. In four pa-

**Table 4.2.** Patient characteristics and tumour characteristics at diagnosis according to initial craniopharyngioma treatment

| | GTR (*n*=25) *n* (%) | STR w/o RTx (*n*=44) *n* (%) | STR with RTx (*n*=25) *n* (%) | Cyst aspiration (*n*=8) *n* (%) | ⁹⁰Yttrium (*n*=21) *n* (%) | *P*-value |
|---|---|---|---|---|---|---|
| **Baseline characteristics** | | | | | | |
| Gender | ♂ 9 (36) ♀ 16 (64) | ♂ 19 (43) ♀ 25 (57) | ♂ 11 (44) ♀ 14 (56) | ♂ 3 (38) ♀ 5 (63) | ♂ 12 (57) ♀ 9 (43) | 0.69 |
| Median age at presentation (yr.) (interquartile range) | 15 (8-37) | 26 (9-41) | 26 (15-46) | 13 (5-71) | 11 (6-45) | 0.38 |
| **Tumour characteristics** | | | | | | |
| Localization: | | | | | | 0.84 |
| - Intrasellar | 1 (4) | 1 (2) | 1 (4) | 0 (0) | 1 (5) | |
| - Suprasellar | 9 (39) | 14 (33) | 9 (38) | 5 (63) | 10 (48) | |
| - Intra-/suprasellar | 13 (57) | 28 (65) | 14 (58) | 3 (38) | 10 (48) | |
| Consistency: | | | | | | 0.81 |
| - Unicystic | 15 (65) | 23 (58) | 15 (65) | 5 (63) | 13 (65) | |
| - Multicystic | 7 (30) | 14 (35) | 6 (26) | 3 (38) | 7 (35) | |
| - Solid | 1 (4) | 3 (8) | 2 (9) | 0 (0) | 0 (0) | |
| Presence of hydrocephalus | 6 (25) | 10 (23) | 5 (21) | 5 (63) | 7 (33) | 0.18 |
| Hypothalamic and/or third ventricle involvement | 11 (48) | 20 (50) | 15 (68) | 6 (75) | 7 (41) | 0.28 |
| Brain stem compression | 2 (9) | 4 (10) | 4 (17) | 1 (13) | 4 (24) | 0.65 |

Data regarding initial craniopharyngioma localization, consistency, hydrocephalus, hypothalamic and/or third ventricle involvement, and brain stem compression were missing in four, nine, three, 13, and 12 patients, respectively. ♂ = male; ♀ = female; % = percentage; ⁹⁰Yttrium = ⁹⁰Yttrium brachytherapy; GTR = gross total resection; *n* = number; RTx = radiotherapy; STR = subtotal resection; w/o = without; yr. = years.

tients, detailed information on the type of radiotherapy was missing. In the patients who initially received radiotherapy, the median cumulative radiation dose was 54 Gy (interquartile range 54-54 Gy); delivered in a median 30 fractions (interquartile range 30-30 fractions). The median duration between neurosurgery and radiotherapy was two months (interquartile range 1-6 months).

In our institution, initial craniopharyngioma treatment changed over time (Figure 4.1). The use of gross total resection declined from 22% in 1980-1989 to 12% in ≥2010. Meanwhile, the use of subtotal resection (with or without radiotherapy) increased from 30% in 1980-1989 to 71% in ≥2010. ⁹⁰Yttrium brachytherapy was predominantly used in 1980-1989.

**Craniopharyngioma therapy per treatment decade**
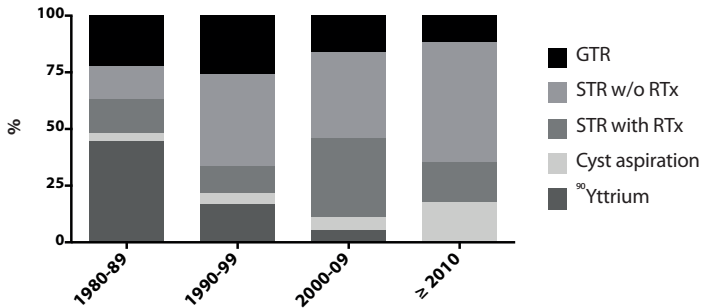


**Figure 4.1.** Initial craniopharyngioma treatment per decade
% = percentage; [90]Yttrium = [90]Yttrium brachytherapy; GTR = gross total resection; RTx = radiotherapy; STR = subtotal resection; w/o = without.

## Long-term health conditions

Long-term health conditions in patients with craniopharyngioma are shown in Table 4.3. Pituitary hormone deficiencies, visual disturbances, and obesity were the most common long-term health effects and affected 98%, 75%, and 56% of the patients, respectively. Hypogonadotropic hypogonadism was the most common pituitary hormone deficiency and was found in 92% of the patients. Diabetes insipidus was diagnosed in 61% of the patients. Five patients demonstrated blindness (four after initial treatment with subtotal resection; one after initial treatment with [90]Yttrium brachytherapy). Severe neurological deficits (i.e. compromising independent daily living) affected 11 patients. In three patients, severe neurological deficits were directly related to the craniopharyngioma itself. One patient developed radiation encephalopathy six years after conventional external beam radiotherapy at an age of 41 years. Three patients suffered from radionecrosis related to leakage of the installed radio-isotope a median 15 months after [90]Yttrium brachytherapy at a median age of 54 years. In four patients, cerebrovascular events caused severe neurological dysfunction a median seven months after initial craniopharyngioma treatment at a median age of 27 years. This latter group included one child who experienced a cerebral infarction of the entire left hemisphere without a known cause approximately two years after craniopharyngioma resection.

Long-term health conditions according to initial craniopharyngioma treatment are shown in Table 4.4. Initial craniopharyngioma treatment with gross total resection, subtotal resection with or without radiotherapy, cyst aspiration, and [90]Yttrium brachytherapy resulted in a similar pattern of long-term health effects. Long-term health conditions in patients with childhood- compared with adult-onset craniopharyngioma are shown in Table 4.3. Patients with childhood-onset craniopharyngioma demonstrated significantly more growth hormone deficiency (93% vs. 68%, $P<0.01$), diabetes insipidus

**Table 4.3.** Long-term health conditions in patients with craniopharyngioma

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

Data regarding visual acuity disorders and visual field defects were missing in 16 and 29 patients, respectively. Weight status could not be determined in 17 patients. Data regarding pituitary hormone deficiencies were missing in six patients (GH in five patients, FSH/LH in one patient, TSH in one patient, anterior PH in six patients, and complete PH in one patient). Eight patients were too young to reliably assess gonadal function. [a]Secondary neoplasms included meningioma (*n*=2), prostate cancer (*n*=2), breast cancer (*n*=2), arachnoid cyst (*n*=2), thyroglossal duct cyst (*n*=1), fibroadenoma (*n*=2), cavernous sinus schwannoma (*n*=1), growth hormone-producing pituitary adenoma (*n*=1), pineal gland cyst (*n*=1), pancreatic cancer (*n*=1), lung cancer (*n*=1), mesothelioma (*n*=1), bladder cancer (*n*=1), ovarian cancer (*n*=1), cervical cancer (*n*=1), calcifying odontogenic cyst (*n*=1), osteoma of the skull (*n*=1), haemangioma (*n*=1), Hodgkin lymphoma (*n*=1), neuro-endocrine tumour of the appendix (*n*=1). % = percentage; BMI = body mass index; kg/m$^2$ = kilograms per square metre; *n* = number; yr. = years.

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

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

**Survival**

Overall and recurrence-/progression-free survival after initial craniopharyngioma treatment are shown in Figure 4.2 and Figure 4.3. Overall survival was 93%, 85%, and 77% at 5, 10, and 20 years of follow-up. Recurrence-/progression-free survival was 90%, 74%, and 52% at 5, 10, and 20 years of follow-up. Although overall survival was comparable after initial craniopharyngioma treatment with gross total resection, subtotal resection with or without radiotherapy, cyst aspiration, and [90]Yttrium brachytherapy, recurrence-/progression-free survival was not (*P*=0.03). Bonferroni-corrected post-hoc analyses revealed a significantly lower recurrence-/progression-free survival after initial craniopharyngioma treatment with cyst aspiration compared with the other treatment approaches (*P*=0.01). Overall and recurrence-/progression-free survival were similar in patients with childhood- and adult-onset craniopharyngioma. Patients with craniopharyngioma recurrence/progression experienced a significantly lower overall survival compared with patients without craniopharyngioma recurrence/progression (*P*<0.01). Initial craniopharyngioma treatment in more recent decades resulted in similar overall survival (*P*=0.50 for trend) and lower recurrence-/progression-free survival (*P*<0.01 for trend). Overall survival was also similar over time in the subgroup of patients with craniopharyngioma recurrence/progression (*P*=0.46 for trend).

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

**Table 4.4.** Long-term health conditions according to initial craniopharyngioma treatment

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

Data regarding visual acuity disorders and visual field defects were missing in 15 and 28 patients, respectively. Weight status could not be determined in 16 patients. Data regarding pituitary hormone deficiencies were missing in five patients (GH in four patients, FSH/LH in one patient, TSH in one patient, anterior PH in five patients, and complete PH in one patient). Eight patients were too young to reliably assess gonadal function. % = percentage; $^{90}$Yttrium = $^{90}$Yttrium brachytherapy; BMI = body mass index; GTR = gross total resection; kg/m$^2$ = kilograms per square metre; *n* = number; RTx = radiotherapy; STR = subtotal resection; w/o = without; yr. = years.

**Figure 4.2.** Overall survival in patients with craniopharyngioma
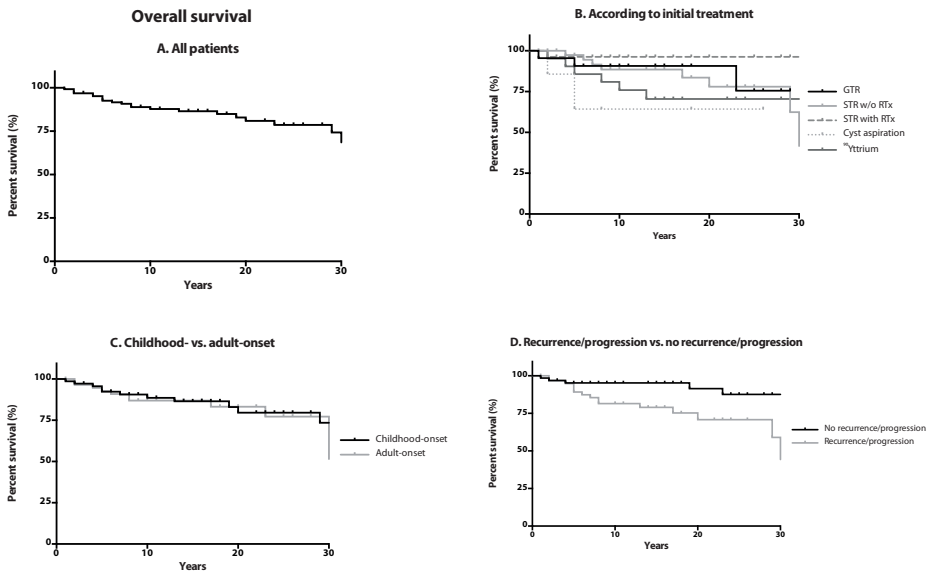


**A:** All patients. **B:** According to initial craniopharyngioma treatment. **C:** Patients with childhood- and adult-onset craniopharyngioma. **D:** According to recurrence/progression status. [90]Yttrium = [90]Yttrium brachyther-apy; GTR = gross total resection; RTx = radiotherapy; STR = subtotal resection; w/o = without.

itself occurred with similar frequencies after initial craniopharyngioma treatment with gross total resection, subtotal resection with or without radiotherapy, cyst aspiration, and [90]Yttrium brachytherapy (*P*=0.90), as well as in patients with childhood- and adult-onset disease (*P*=0.28).

## DISCUSSION

In this large single-centre study of patients with craniopharyngioma treated from 1980 onwards, we cross-sectionally analysed retrospectively collected data on a full spectrum of long-term health conditions. After a median follow-up of 13 years since presentation, we observed a similar pattern of long-term health effects after initial craniopharyngioma treatment with gross total resection, subtotal resection with or without radiotherapy, cyst aspiration, and [90]Yttrium brachytherapy. In general, long-term health conditions were more frequent in patients with childhood- compared with adult-onset craniopha-ryngioma.

Pituitary hormone deficiencies, visual disturbances, and obesity were the most fre-quently observed long-term health conditions in our study. This is in concordance with other studies that reported prevalence rates of 78-100% for pituitary hormone deficien-

**Recurrence-/progression-free survival**



**A. All patients**



**B. According to initial treatment**

**Figure 4.3.** Recurrence-/progression-free survival in patients with craniopharyngioma
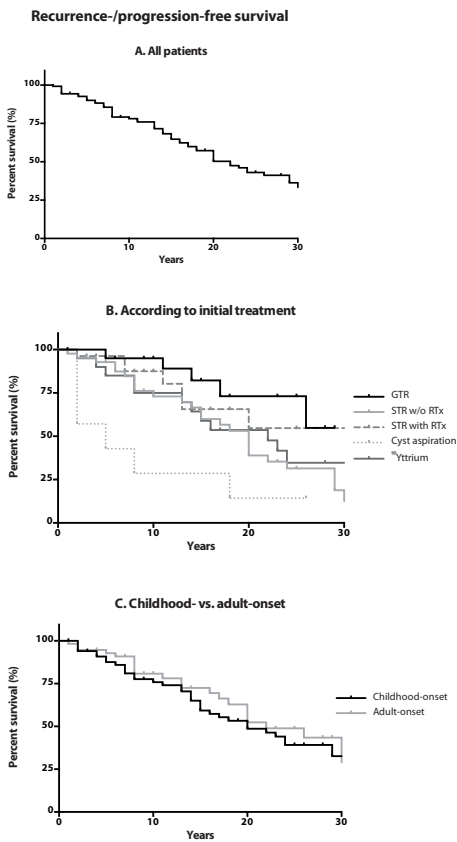**A:** All patients. **B:** According to initial craniopharyngioma treatment. **C:** Patients with childhood- and adult-onset craniopharyngioma. $^{90}$Yttrium = $^{90}$Yttrium brachytherapy; GTR = gross total resection; RTx = radiotherapy; STR = subtotal resection; w/o = without.

**C. Childhood- vs. adult-onset**



cies, 49-87% for visual disturbances, and 27-57% for obesity.[10, 20, 22, 23, 26, 28, 30, 32] Notably, we observed a relatively high frequency of obstructive sleep apnoea (i.e. 9%) in patients with craniopharyngioma. This is considerably higher than the prevalence of obstructive sleep apnoea in the Dutch general population, which is estimated to be 1-4%.[38] Since only patients with suspected sleep disordered breathing were evaluated for obstructive sleep apnoea in our study, the observed frequency of 9% may even be an underestimation of the real prevalence of obstructive sleep apnoea in patients with craniopharyngioma. Only a few other studies compared long-term health conditions in patients with craniopharyngioma according to initial treatment approach.[17, 35-37] In concordance with our results, these studies observed no important differences in long-term health effects after different initial craniopharyngioma treatment approaches. Lo et al. only observed a higher frequency of diabetes insipidus after initial craniopharyngioma treatment with neurosurgery compared with craniopharyngioma treatment without neurosurgery in 123 patients after a median follow-up of 9 years.[35] Karavitaki et al. only observed more

visual field defects after initial craniopharyngioma treatment with subtotal resection without radiotherapy compared with craniopharyngioma treatment with gross total resection or subtotal resection with radiotherapy in 121 patients after a mean follow-up of 9 years.[36] Schoenfeld et al. only observed a higher rate of diabetes insipidus and panhypopituitarism after initial craniopharyngioma treatment with gross total resection compared with subtotal resection with or without radiotherapy in 122 patients after a median follow-up of 5 years.[17] Merchant et al. only observed more diabetes insipidus and less hypogonadotropic hypogonadism after initial craniopharyngioma treatment with gross total resection compared with subtotal resection with radiotherapy in 30 patients after a median follow-up of 6 years.[37]

In our study, long-term health conditions seemed to occur more frequently in patients with childhood- compared with adult-onset craniopharyngioma. This may be explained by differences in tumour characteristics between patients with childhood- and adult-onset craniopharyngioma already present at diagnosis. In our study, patients with childhood-onset craniopharyngioma presented more often with multicystic tumours, as well as tumours associated with hydrocephalus and hypothalamic and/or third ventricle involvement compared with patients with adult-onset craniopharyngioma. In contrast, we observed significantly more cardio- and cerebrovascular events in patients with adult- compared with childhood-onset disease. This may be due to the significantly older age at follow-up of patients with adult-onset craniopharyngioma. Aging has been established as an important risk factor for cardio- and cerebrovascular disease.[39] Several other studies compared long-term health conditions between patients with childhood- and adult-onset craniopharyngioma.[28, 30, 36] In concordance with our results, Gautier et al. observed a significantly higher prevalence of diabetes insipidus and panhypopituitarism in patients with childhood- compared with adult-onset disease in a cohort of 171 patients derived from two academic centres in France after a median follow-up of 12 years.[30] In contrast, Kendall-Taylor et al. observed a significantly higher frequency of obesity in patients with adult- compared with childhood-onset craniopharyngioma. In their study, which included 393 growth hormone-deficient patients from the KIMS (Pfizer International Metabolic Database) who were followed for a mean 17 years, frequencies of any pituitary hormone deficiency and panhypopituitarism were similar between patients with childhood- and adult-onset disease.[28] The aforementioned study by Karavitaki et al. did not observe any significant differences in long-term health conditions between patients with childhood- and adult-onset craniopharyngioma, except for complete dependency for activities of daily living, which was more common in patients with adult-onset craniopharyngioma.[36]

We observed 10-year overall and recurrence-/progression-free survival rates after initial craniopharyngioma treatment of 85% and 74%, respectively. This is comparable to other studies in patients with craniopharyngioma that reported 10-year overall and

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

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

Strengths of our study include the full spectrum of long-term health conditions investigated, as well as the relatively large number of patients treated with [90]Yttrium brachytherapy assessed. Brachytherapy was first introduced as a treatment for craniopharyngioma in 1952 by Leksell and Liden, and involves the minimally-invasive stereotactic application of beta-emitting isotopes in craniopharyngioma cysts.[40] Subsequent radiation-induced destruction of epithelial cyst lining results in cyst shrinkage.[41] Due to the short half-value depth of [90]Yttrium in soft tissue, [90]Yttrium brachytherapy is not ef-

fective for solid craniopharyngiomas.[42] Only a few other studies investigated long-term health conditions after craniopharyngioma treatment with [90]Yttrium brachytherapy.[42-44] These studies reported somewhat lower frequencies of long-term health effects compared with our study (55-90% for pituitary hormone deficiencies, 61-90% for visual disturbances, and 51% for obesity). This may be explained by a longer follow-up duration after [90]Yttrium brachytherapy in our study (22 years vs. 3-12 years in the other studies). Besides these strengths, some limitations should be considered when interpreting the results of our study. The retrospective nature of data collection may predispose to selection bias and missing data. However, due to the rarity of craniopharyngioma and the prolonged follow-up duration required to adequately study long-term health conditions, it seems unlikely that prospective observational studies with an adequate follow-up duration and a sufficient number of patients will become available in the near future. In addition, neuroimaging techniques were less sensitive in earlier compared with more recent decades. This may have biased the assessment of the degree of craniopharyngioma resection, especially during earlier decades. Furthermore, our results on long-term neurocognitive and neuropsychological sequelae should be interpreted with caution, as cognitive impairments and behavioral changes were considered present when documented in the patient files and have not been formally tested. Moreover, we were unable to compare long-term health conditions according to histological subtype of craniopharyngioma (i.e. adamantinomatous or papillary), since these data were only available in a minority of patients.

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

## REFERENCES

1.  Muller HL. Craniopharyngioma. *Endocr Rev* 2014 **35** 513-543.
2.  Nielsen EH, Feldt-Rasmussen U, Poulsgaard L, Kristensen LO, Astrup J, Jorgensen JO, Bjerre P, Andersen M, Andersen C, Jorgensen J, Lindholm J & Laurberg P. Incidence of craniopharyngioma in Denmark (n = 189) and estimated world incidence of craniopharyngioma in children and adults. *J Neurooncol* 2011 **104** 755-763.
3.  Von Zenker AF. Enorme Zystenbildung im Gehirn, vom Hirnanhang ausgehend. *Arch Pathol Anat Physiol Klin Med* 1857 **2** 454–466.
4.  Barkhoudarian G & Laws ER. Craniopharyngioma: history. *Pituitary* 2013 **16** 1-8.
5.  Karavitaki N. Management of craniopharyngiomas. *J Endocrinol Invest* 2014 **37** 219-228.
6.  Buchfelder M, Schlaffer SM, Lin F & Kleindienst A. Surgery for craniopharyngioma. *Pituitary* 2013 **16** 18-25.
7.  Mortini P, Losa M, Pozzobon G, Barzaghi R, Riva M, Acerno S, Angius D, Weber G, Chiumello G & Giovanelli M. Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series. *J Neurosurg* 2011 **114** 1350-1359.
8.  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. *J Neurosurg Pediatr* 2010 **5** 30-48.
9.  Zhang YQ, Ma ZY, Wu ZB, Luo SQ & Wang ZC. Radical resection of 202 pediatric craniopharyngiomas with special reference to the surgical approaches and hypothalamic protection. *Pediatr Neurosurg* 2008 **44** 435-443.
10. Du C, Feng CY, Yuan XR, Liu Q, Peng ZF, Jiang XJ, Li XJ, Xiao GL, Li YF & Xiong T. Microsurgical management of craniopharyngiomas via an unilateral subfrontal approach - a retrospective study of 177 continuous cases. *World Neurosurg* 2016.
11. Bal E, Oge K & Berker M. Endoscopic Endonasal Transsphenoidal Surgery, a Reliable Method for Treating Primary and Recurrent/Residual Craniopharyngiomas: Nine Years of Experience. *World Neurosurg* 2016.
12. Xing H, Xing H, Hui P & Yang B. Removal of craniopharyngioma via fronto-basal interhemispheric approach. *Oncol Lett* 2016 **12** 147-149.
13. Cheng J, Shao Q, Pan Z & You J. Analysis and Long-Term Follow-Up of the Surgical Treatment of Children With Craniopharyngioma. *J Craniofac Surg* 2016 **27** e763-e766.
14. Moussazadeh N, Prabhu V, Bander ED, Cusic RC, Tsiouris AJ, Anand VK & Schwartz TH. Endoscopic endonasal versus open transcranial resection of craniopharyngiomas: a case-matched single-institution analysis. *Neurosurg Focus* 2016 **41** E7.
15. Morisako H, Goto T, Goto H, Bohoun CA, Tamrakar S & Ohata K. Aggressive surgery based on an anatomical subclassification of craniopharyngiomas. *Neurosurg Focus* 2016 **41** E10.
16. Winkfield KM, Tsai HK, Yao X, Larson E, Neuberg D, Pomeroy SL, Ullrich NJ, Cohen LE, Kieran MW, Scott RM, Goumnerova LC & Marcus KJ. Long-term clinical outcomes following treatment of childhood craniopharyngioma. *Pediatr Blood Cancer* 2011 **56** 1120-1126.
17. Schoenfeld A, Pekmezci M, Barnes MJ, Tihan T, Gupta N, Lamborn KR, Banerjee A, Mueller S, Chang S, Berger MS & Haas-Kogan D. The superiority of conservative resection and adjuvant radiation for craniopharyngiomas. *J Neurooncol* 2012 **108** 133-139.
18. Schubert T, Trippel M, Tacke U, van Velthoven V, Gumpp V, Bartelt S, Ostertag C & Nikkhah G. Neurosurgical treatment strategies in childhood craniopharyngiomas: is less more? *Childs Nerv Syst* 2009 **25** 1419-1427.

19.  Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, Zerah M, Bezerra M, Renier D, Pierre-Kahn A & Sainte-Rose C. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. *J Neurosurg* 2007 **106** 3-12.

20.  Tan TS, Patel L, Gopal-Kothandapani JS, Ehtisham S, Ikazoboh EC, Hayward R, Aquilina K, Skae M, Thorp N, Pizer B, Didi M, Mallucci C, Blair JC, Gaze MN, Kamaly-Asl I, Spoudeas H & Clayton PE. The neuroendocrine sequelae of paediatric craniopharyngioma: a 40 year meta-data analysis of 185 cases from three UK centres. *Eur J Endocrinol* 2017.

21.  Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, Bates AS & Stewart PM. Mortality in patients with pituitary disease. *Endocr Rev* 2010 **31** 301-342.

22.  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. *J Clin Endocrinol Metab* 2015 **100** 467-474.

23.  Lee CC, Yang HC, Chen CJ, Hung YC, Wu HM, Shiau CY, Guo WY, Pan DH, Chung WY & Liu KD. Gamma Knife surgery for craniopharyngioma: report on a 20-year experience. *J Neurosurg* 2014 **121 Suppl** 167-178.

24.  Pan J, Qi S, Liu Y, Lu Y, Peng J, Zhang X, Xu Y, Huang GL & Fan J. Growth patterns of craniopharyngiomas: clinical analysis of 226 patients. *J Neurosurg Pediatr* 2016 **17** 418-433.

25.  Hoffmann A, Warmuth-Metz M, Lohle K, Reichel J, Daubenbuchel AM, Sterkenburg AS & Muller HL. Fusiform dilatation of the internal carotid artery in childhood-onset craniopharyngioma: multicenter study on incidence and long-term outcome. *Pituitary* 2016.

26.  Elliott RE, Jane JA, Jr. & Wisoff JH. Surgical management of craniopharyngiomas in children: meta-analysis and comparison of transcranial and transsphenoidal approaches. *Neurosurgery* 2011 **69** 630-643; discussion 643.

27.  Honegger J, Buchfelder M & Fahlbusch R. Surgical treatment of craniopharyngiomas: endocrinological results. *J Neurosurg* 1999 **90** 251-257.

28.  Kendall-Taylor P, Jonsson PJ, Abs R, Erfurth EM, Koltowska-Haggstrom M, Price DA & Verhelst J. 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** 557-567.

29.  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** 1029-1038.

30.  Gautier A, Godbout A, Grosheny C, Tejedor I, Coudert M, Courtillot C, Jublanc C, De Kerdanet M, Poirier JY, Riffaud L, Sainte-Rose C, Van Effenterre R, Brassier G, Bonnet F, Touraine P & Craniopharyngioma Study G. Markers of recurrence and long-term morbidity in craniopharyngioma: a systematic analysis of 171 patients. *J Clin Endocrinol Metab* 2012 **97** 1258-1267.

31.  Wijnen M, Olsson DS, van den Heuvel-Eibrink MM, Wallenius V, Janssen J, Delhanty PJ, van der Lely AJ, Johannsson G & Neggers S. Efficacy and safety of bariatric surgery for craniopharyngioma-related hypothalamic obesity-A matched case-control study with two years of follow-up. *Int J Obes (Lond)* 2016.

32.  Muller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, Korinthenberg R, Bettendorf M, Kuhl J, Gutjahr P, Sorensen N & Calaminus G. Obesity after childhood craniopharyngioma--German multicenter study on pre-operative risk factors and quality of life. *Klin Padiatr* 2001 **213** 244-249.

33.  Smith TR, Cote DJ, Jane JA, Jr. & Laws ER, Jr. Physiological growth hormone replacement and rate of recurrence of craniopharyngioma: the Genentech National Cooperative Growth Study. *J Neurosurg Pediatr* 2016 **18** 408-412.

34.  Rao YJ, Hassanzadeh C, Fischer-Valuck B, Chicoine MR, Kim AH, Perkins SM & Huang J. Patterns of care and treatment outcomes of patients with Craniopharyngioma in the national cancer database. *J Neurooncol* 2016.

35.  Lo AC, Howard AF, Nichol A, Sidhu K, Abdulsatar F, Hasan H & Goddard K. Long-term outcomes and complications in patients with craniopharyngioma: the british columbia cancer agency experience. *Int J Radiat Oncol Biol Phys* 2014 **88** 1011-1018.

36.  Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, Shine B, Turner HE & Wass JA. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol (Oxf)* 2005 **62** 397-409.

37.  Merchant TE, Kiehna EN, Sanford RA, Mulhern RK, Thompson SJ, Wilson MW, Lustig RH & Kun LE. Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984-2001. *Int J Radiat Oncol Biol Phys* 2002 **53** 533-542.

38.  Damen-van Beek Z, Lucassen PL, Gorgels W, Smelt AF, Knuistingh Neven A & Bouma M. [The NHG guideline 'Sleep problems and sleeping pills']. *Ned Tijdschr Geneeskd* 2015 **159** A8679.

39.  Sniderman AD & Furberg CD. Age as a modifiable risk factor for cardiovascular disease. *Lancet* 2008 **371** 1547-1549.

40.  Leksell L & Liden K. A therapeutic trial with radioactive isotopes in cystic brain tumour. Radioisotope techniques I. *Med Physiol Appl* 1952 1-4.

41.  Szeifert GT, Balint K, Sipos L, Sarker MH, Czirjak S & Julow J. Pathological findings in cystic craniopharyngiomas after stereotactic intracavitary irradiation with yttrium-90 isotope. *Prog Neurol Surg* 2007 **20** 297-302.

42.  Van den Berge JH, Blaauw G, Breeman WA, Rahmy A & Wijngaarde R. Intracavitary brachytherapy of cystic craniopharyngiomas. *J Neurosurg* 1992 **77** 545-550.

43.  Voges J, Sturm V, Lehrke R, Treuer H, Gauss C & Berthold F. Cystic craniopharyngioma: long-term results after intracavitary irradiation with stereotactically applied colloidal beta-emitting radioactive sources. *Neurosurgery* 1997 **40** 263-269; discussion 269-270.

44.  Julow JV. Intracystic irradiation for craniopharyngiomas. *Pituitary* 2013 **16** 34-45.

# Chapter 5

## Excess morbidity and mortality in patients with craniopharyngioma: A hospital-based retrospective cohort study

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## ABSTRACT

**Objective:** Most studies in patients with craniopharyngioma did not investigate morbidity and mortality relative to the general population, nor evaluated risk factors for excess morbidity and mortality. Therefore, the objective of this study was to examine excess morbidity and mortality, as well as their determinants in patients with craniopharyngioma.

**Design:** Hospital-based retrospective cohort study conducted between 1987-2014.

**Methods:** We included 144 Dutch and 80 Swedish patients with craniopharyngioma identified by a computer-based search in the medical records (105 females [47%], 112 patients with childhood-onset craniopharyngioma [50%], 3153 person-years of follow-up). Excess morbidity and mortality were analysed using standardized incidence and mortality ratios (SIRs and SMRs). Risk factors were evaluated univariably by comparing SIRs and SMRs between non-overlapping subgroups.

**Results:** Patients with craniopharyngioma experienced excess morbidity due to type 2 diabetes mellitus (SIR 4.4, 95% confidence interval [CI] 2.8-6.8) and cerebral infarction (SIR 4.9, 95%CI 3.1-8.0) compared to the general population. Risks for malignant neoplasms, myocardial infarctions, and fractures were not increased. Patients with craniopharyngioma also had excess total mortality (SMR 2.7, 95%CI 2.0-3.8), and mortality due to circulatory (SMR 2.3, 95%CI 1.1-4.5) and respiratory (SMR 6.0, 95%CI 2.5-14.5) diseases. Female sex, childhood-onset craniopharyngioma, hydrocephalus, and tumour recurrence were identified as risk factors for excess type 2 diabetes mellitus, cerebral infarction, and total mortality.

**Conclusions:** Patients with craniopharyngioma are at increased risk for type 2 diabetes mellitus, cerebral infarction, total mortality, and mortality due to circulatory and respiratory diseases. Female sex, childhood-onset craniopharyngioma, hydrocephalus, and tumour recurrence are important risk factors.

## INTRODUCTION

Craniopharyngiomas are benign epithelial tumours located in the (supra)sellar area of the skull that often contain calcifications and fluid-filled cysts. Their locally aggressive behaviour and proximity to critical neurovascular structures (e.g. hypothalamus, pituitary, optic nerves, and carotid arteries) characterize them as challenging tumours.[1] Craniopharyngiomas are rare with an estimated incidence rate of 1.7 per million person-years.[2] They affect both children and adults, and have peak incidences between 5-9 and 40-44 years of age.[3] Craniopharyngiomas are generally treated with neurosurgery, which is sometimes followed by radiotherapy.[1] Despite encouraging 10-year overall survival rates between 77-93%,[2, 4-7] long-term tumour- and treatment-related morbidity is common.[2, 5-14] Hypopituitarism, visual impairment, and obesity are the most frequently observed long-term health conditions in patients with craniopharyngioma.[6-11, 14]

Although previous studies have examined morbidity and mortality in patients with craniopharyngioma, only a few investigated morbidity and mortality in relation to the general population. To our knowledge, only one previous study examined excess morbidity,[2] and only six previous studies investigated excess mortality in patients with craniopharyngioma relative to a background population.[2, 15-19] The study examining excess morbidity observed significantly increased standardized incidence ratios (SIRs) for type 2 diabetes mellitus (T2DM), fractures, infections, cerebral infarction, and visual impairment.[2] The studies that investigated excess mortality reported significantly increased standardized mortality ratios (SMRs) for total mortality between 2.5-9.3.[2, 15-19] Many of these studies were limited by a sample size too small to assess cause-specific mortality. The increased risk for morbidity and mortality in patients with craniopharyngioma is likely to be multifactorial, and include tumour- and treatment-related damage of critical neurovascular structures, as well as their associated health conditions. To date, only three previous studies reported risk factors for excess morbidity and mortality in patients with craniopharyngioma.[2, 15, 17] These studies evaluated only a few potential risk factors but identified female sex, childhood-onset disease, and panhypopituitarism as significant determinants of excess morbidity and mortality.

The objective of our study was to examine morbidity and mortality in patients with craniopharyngioma in relation to the general population. In addition, the objective was to identify risk factors for excess morbidity and mortality in patients with craniopharyngioma.

## MATERIALS AND METHODS

### Study population

We performed a hospital-based retrospective cohort study with data from patients treated for craniopharyngioma at the Erasmus University Medical Centre (Rotterdam, the Netherlands) and the Sahlgrenska University Hospital (Gothenburg, Sweden). We conducted our study between 1987-2014 because Swedish general population data on morbidity and mortality were only available for this period. To increase the strength of our study, we also included patients with craniopharyngioma treated before 1987. These patients entered the study on 1st January 1987. A computer-based search in the medical records identified 224 patients with craniopharyngioma (144 Dutch and 80 Swedish patients) of whom 53 patients (24%) were treated before 1987. The local institutional review board of the Erasmus University Medical Centre and the regional ethical review board in Gothenburg, Sweden, approved this study. All patients gave their informed consent.

### Morbidity and mortality

Data on morbidity and mortality in patients with craniopharyngioma were collected from the medical records. Data on mortality from the Dutch general population were derived from Statistics Netherlands; data on morbidity and mortality from the Swedish general population from the Swedish National Patient Registry, the Swedish Cancer Registry, and the Swedish National Cause of Death Registry. Data on morbidity from the Dutch general population were unavailable. Therefore, we used Swedish general population data to examine excess morbidity in Dutch patients with craniopharyngioma. Morbidity and cause-specific mortality were categorized according to the International Classification of Diseases, Tenth Revision (ICD-10) (see Supplementary data). Malignant neoplasms, T2DM, myocardial infarction, cerebral infarction, and fractures were studied as morbidities. Cause-specific mortality was studied for circulatory diseases (ICD-10 chapter 9) and respiratory diseases (ICD-10 chapter 10). In addition, cause-specific mortality was examined for a few particular conditions (i.e. malignant neoplasms, ischemic heart disease, and cerebrovascular disease). Baseline, tumour, and treatment characteristics, as well as craniopharyngioma recurrence, panhypopituitarism, and weight status at last available follow-up visit were studied as risk factors for excess morbidity and mortality. Hypothalamic damage was defined as tumour- and/or treatment-related injury to the hypothalamus and/or third ventricle as documented in neuroimaging and/or neurosurgery reports. Craniopharyngioma recurrence was defined as reappearance or re-growth of the tumour after prior treatment. Panhypopituitarism was diagnosed based on formal pituitary function testing in all patients. Weight status was classified into obese (i.e. body mass index $\geq 30$ kg/m$^2$) and non-obese (i.e. body mass index $<30$ kg/m$^2$).

## Statistics

Morbidity and mortality were studied as events and compared between patients with craniopharyngioma and the general population using SIRs and SMRs. SIRs and SMRs were calculated as the ratio of the observed to the expected number of events encountered during the study period, as measured in person-years. Corresponding 95% confidence intervals (CIs) were calculated assuming a Poisson distribution of the observed number of events. Person-years were calculated from the date of study entry to the date of an event or end of study (i.e. 31st December 2014). General population data stratified according to sex, five-year age group, and one-year calendar period were used to calculate the expected number of events. SIRs were calculated depending on whether the patient was diagnosed with a specific morbidity on a yearly basis, except for the diagnosis of T2DM, which was assessed at the first event only. SIRs and SMRs were not calculated in case less than three events were observed. Risk factors for excess morbidity and mortality were evaluated univariably by comparing SIRs and SMRs between non-overlapping subgroups.[20] Relevant comparisons were also conducted with the exclusion of patients who died within the first six months after their initial craniopharyngioma treatment to account for survivorship bias. A *P*-value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS (version 24) and Stata (version 14).

## RESULTS

### Patient characteristics

We included 224 patients with craniopharyngioma (105 females [47%]) (Table 5.1). Craniopharyngiomas presented <18 years of age (i.e. childhood-onset) in 112 patients (50%). Patients were followed-up for a median period of 13 years (interquartile range 6-21), representing 3153 person-years. Median age at end of study was 42 years (interquartile range 27-59). Growth hormone replacement therapy was used by 78% of patients with growth hormone deficiency. Sex steroid replacement therapy was used by 92% of males and premenopausal females with hypogonadotropic hypogonadism. In patients with secondary adrenal insufficiency, the median daily hydrocortisone equivalent dose was 20 milligrams (interquartile range 20-22.5). Patient characteristics were similar in females compared to males, except for hypertension (51% vs. 33%; *P*<0.05) and dyslipidaemia (29% vs. 16%; *P*<0.05).

### Excess morbidity

Excess morbidity and their risk factors in patients with craniopharyngioma are shown in Figure 5.1 and Table 5.2, respectively. Twenty patients with craniopharyngioma were diagnosed with T2DM compared to the expected number of 4.6, resulting in a significantly

**Table 5.1.** Patient characteristics[a]

| | All patients (*n*=224) | Females (*n*=105) | Males (*n*=119) |
|---|---|---|---|
| **Baseline characteristics** | | | |
| Age at presentation (years)[b] | 20 (9-42) | 20 (10-41) | 20 (8-42) |
|    Childhood-onset (*n* [%]) | 112 (50) | 53 (50) | 59 (50) |
|    Adult-onset (*n* [%]) | 112 (50) | 42 (40) | 60 (50) |
| Follow-up (years)[b] | 13 (6-21) | 14 (7-22) | 12 (6-21) |
| Age at end of study (years)[b] | 42 (27-59) | 42 (27-57) | 41 (26-60) |
| **Tumour characteristics** | | | |
| Location (*n* [%]) | | | |
|    Intrasellar | 5 (2) | 1 (1) | 4 (4) |
|    Suprasellar | 87 (41) | 40 (40) | 47 (42) |
|    Intra-/suprasellar | 120 (57) | 58 (59) | 62 (55) |
| Hydrocephalus (*n* [%]) | 62 (28) | 32 (31) | 30 (26) |
| Hypothalamic damage (*n* [%]) | 90 (43) | 43 (43) | 47 (43) |
| **Craniopharyngioma treatment** | | | |
| Neurosurgery (*n* [%]) | 210 (94) | 99 (94) | 111 (93) |
|    Complete resection | 69 (39) | 30 (36) | 39 (42) |
|    Incomplete resection | 106 (61) | 53 (64) | 53 (58) |
| Radiotherapy (*n* [%]) | 101 (45) | 48 (46) | 53 (45) |
| Recurrence (*n* [%]) | 89 (40) | 45 (43) | 44 (38) |
| **Long-term health conditions** | | | |
| Pituitary hormone deficiencies (*n* [%]) | 215 (96) | 100 (95) | 115 (97) |
|    GH | 180 (83)[e] | 85 (82) | 95 (83) |
|      GH dose (mg/day)[b] | 0.4 (0.3-0.8) | 0.5 (0.3-0.8) | 0.4 (0.3-0.7) |
|    FSH/LH | 183 (85)[f] | 86 (86) | 97 (84) |
|    TSH | 202 (91)[g] | 92 (89) | 110 (92) |
|    ACTH | 183 (82)[g] | 83 (79) | 100 (84) |
|      HC equivalent dose (mg/day)[b] | 20 (20-22.5) | 20 (16-20) | 20 (20-25) |
|    ADH | 141 (63)[g] | 69 (66) | 72 (61) |
|    Panhypopituitarism | 114 (51) | 58 (55) | 56 (48) |
| Visual impairment (*n* [%])[c] | 156 (77) | 72 (76) | 84 (79) |
| Obesity (*n* [%]) | 101 (50) | 52 (54) | 49 (47) |
| Hypertension (*n* [%]) | 76 (41) | 44 (51) | 32 (33) |
| Dyslipidaemia (*n* [%])[d] | 47 (22) | 28 (29) | 19 (16) |

[a]Evaluations were based on the number of patients with available data. [b]Median (interquartile range). [c]Defined as a decreased visual acuity after correction for refraction disorder and/or as the presence of a visual field defect. [d]Defined as the use of lipid-lowering drugs. [e]Growth hormone replacement therapy was used by 141 patients with growth hormone deficiency (78%). [f]Sex steroid replacement therapy was used by 143 patients with hypogonadotropic hypogonadism (92% of males and premenopausal females). [g]All patients used hormone replacement therapy. ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; FSH/LH = follicle stimulating hormone/luteinizing hormone; GH = growth hormone; HC = hydrocortisone; mg = milligrams; *n* = number; TSH = thyroid stimulating hormone.

**Figure 5.1.** Excess morbidity and mortality in patients with craniopharyngioma

### Morbidity in patients with craniopharyngioma

|  | O | E | SIR (95%CI) |
|---|---|---|---|
| Malignant neoplasms[a] | 10 | 11.3 | 0.9 (0.5-1.6) |
| T2DM | 20 | 4.6 | 4.4 (2.8-6.8) |
| Myocardial infarction | 7 | 4.8 | 1.5 (0.7-3.1) |
| Cerebral infarction | 17 | 3.4 | 4.9 (3.1-8.0) |
| Fractures | 14 | 11.5 | 1.2 (0.7-2.1) |

Standardized incidence ratio ± 95%CI

**A:** Morbidity.

### Mortality in patients with craniopharyngioma

**Total mortality**

|  | O | E | SMR (95%CI) |
|---|---|---|---|
| Total mortality | 34 | 12.4 | 2.7 (2.0-3.8) |

**Cause-specific mortality**

*ICD-10 chapters*

| Circulatory diseases (chapter 9) | 8 | 3.5 | 2.3 (1.1-4.5) |
|---|---|---|---|
| Respiratory diseases (chapter 10) | 5 | 0.8 | 6.0 (2.5-14.5) |

*Particular conditions*

| Malignant neoplasms | 4 | 4.6 | 0.9 (0.3-2.3) |
|---|---|---|---|
| Ischemic heart disease | 4 | 3.5 | 1.1 (0.4-3.0) |
| Cerebrovascular disease | 4 | 0.7 | 5.8 (2.2-15.5) |

Standardized mortality ratio ± 95%CI

**B:** Mortality. [a]Observed malignant neoplasms included breast cancer (*n*=1), malignant brain tumour (*n*=1), melanoma (*n*=1), mesothelioma (*n*=1), neuro-endocrine tumour of the appendix (*n*=1), ovarian cancer (*n*=1), pancreatic cancer (*n*=1), prostate cancer (*n*=3). CI = confidence interval; E = expected; O = observed; SIR = standardized incidence ratio; SMR = standardized mortality ratio; T2DM = type 2 diabetes mellitus.

increased SIR of 4.4 (95%CI 2.8-6.8). The excess risk for T2DM was significantly higher in patients with female sex, childhood-onset craniopharyngioma, hydrocephalus, hypothalamic damage, incomplete tumour resection, radiotherapy, tumour recurrence, panhypopituitarsm, and obesity. We also observed a significantly increased risk for cerebral infarction in patients with craniopharyngioma (SIR 4.9, 95%CI 3.1-8.0). The excess risk for cerebral infarction was significantly higher in patients with female sex, childhood-onset craniopharyngioma, hydrocephalus, and tumour recurrence. Patients

**Table 5.2.** Risk factors for excess morbidity in patients with craniopharyngioma

| Risk factors | SIR (95%CI) Malignant neoplasms | P | SIR (95%CI) T2DM | P | SIR (95%CI) Myocardial infarction | P | SIR (95%CI) Cerebral infarction | P | SIR (95%CI) Fractures | P |
|---|---|---|---|---|---|---|---|---|---|---|
| Female | 1.1 (0.4-2.5) | 0.62 | 7.3 (3.9-13.5) | <0.05 | 3.4 (1.1-10.5) | 0.11 | 8.1 (4.1-16.2) | <0.05 | 1.7 (0.8-3.5) | 0.31 |
| Male | 0.8 (0.3-1.8) | | 3.1 (1.7-5.8) | | 1.0 (0.4-2.7) | | 3.7 (1.9-7.1) | | 1.0 (0.5-2.0) | |
| Childhood-onset | NC | NC | 10.7 (5.4-21.4) | <0.05 | NC | NC | 16.0 (6.7-38.4) | <0.05 | 1.3 (0.6-2.8) | 0.76 |
| Adult-onset | 0.8 (0.4-1.7) | | 3.1 (1.8-5.5) | | 1.4 (0.6-3.1) | | 3.8 (2.2-6.8) | | 1.1 (0.5-2.4) | |
| Hydrocephalus | NC | NC | 10.1 (4.5-22.4) | <0.05 | NC | NC | 14.6 (6.6-32.5) | <0.05 | 1.2 (0.4-3.8) | 1.00 |
| No hydrocephalus | 0.9 (0.4-1.7) | | 3.7 (2.2-6.3) | | 1.2 (0.5-3.0) | | 3.9 (2.1-7.0) | | 1.2 (0.7-2.3) | |
| Hypothalamic damage | 0.9 (0.3-2.9)[a] | 1.00 | 8.4 (4.3-16.1)[b] | <0.05 | 2.3 (0.7-7.0)[d] | 0.32 | 5.5 (2.5-12.3)[f] | 0.83 | NC | NC |
| No hypothalamic damage | 0.9 (0.4-1.9) | | 3.3 (1.8-6.2) | | 1.0 (0.3-3.2) | | 4.9 (2.6-9.0) | | 1.8 (1.0-3.2) | |
| Complete resection | 1.7 (0.7-4.0)[a] | 0.18 | 2.6 (1.0-6.9)[c] | <0.05 | NC[e] | NC | 4.7 (2.0-11.4)[g] | 0.97 | 0.8 (0.3-2.4)[h] | 0.54 |
| Incomplete resection | 0.7 (0.3-2.0) | | 7.1 (4.2-11.9) | | 2.1 (0.8-5.7) | | 4.8 (2.3-10.0) | | 1.2 (0.6-2.7) | |
| Radiotherapy | 1.2 (0.5-2.7) | 0.32 | 6.8 (4.0-11.5) | <0.05 | 1.9 (0.7-5.0) | 0.47 | 4.9 (2.3-10.2) | 0.97 | 0.9 (0.4-2.2) | 0.34 |
| No radiotherapy | 0.6 (0.2-1.7) | | 2.4 (1.1-5.3) | | 1.1 (0.4-3.5) | | 5.0 (2.7-9.3) | | 1.5 (0.8-2.8) | |
| Recurrence | 1.1 (0.4-2.8) | 0.61 | 6.5 (3.5-12.2) | <0.05 | 2.0 (0.6-6.1)[d] | 0.33 | 8.0 (4.2-15.3)[f] | <0.05 | NC[i] | NC |
| No recurrence | 0.8 (0.4-1.8) | | 3.3 (1.8-6.2) | | 0.9 (0.3-2.8) | | 3.0 (1.5-6.4) | | 1.5 (0.8-2.7) | |
| Panhypopituitarism | 0.7 (0.2-2.2) | 0.62 | 7.3 (4.1-12.8) | <0.05 | 2.1 (0.7-6.4) | 0.45 | 6.9 (3.3-14.4) | 0.29 | 1.1 (0.5-2.4) | 0.75 |
| No panhypopituitarism | 1.0 (0.5-2.1) | | 2.7 (1.4-5.5) | | 1.2 (0.5-3.2) | | 4.1 (2.2-7.7) | | 1.3 (0.7-2.7) | |
| Obesity | 0.6 (0.2-1.9)[a] | 0.46 | 8.8 (5.3-14.7)[d] | <0.05 | 2.4 (0.9-6.3)[d] | NC | 5.6 (2.7-11.8)[f] | 0.70 | 1.0 (0.4-2.3)[i] | 0.48 |
| No obesity | 1.0 (0.5-2.3) | | 1.9 (0.8-4.7) | | NC | | 4.6 (2.4-8.8) | | 1.5 (0.7-2.9) | |
| Treated <1987 | 0.8 (0.2-2.4) | 0.76 | 1.8 (0.6-5.5) | <0.05 | 2.1 (0.7-6.7) | 0.47 | 4.8 (1.8-12.7) | 0.94 | 2.2 (1.1-4.2) | <0.05 |
| Treated ≥1987 | 1.0 (0.5-2.0) | | 5.9 (3.7-9.5) | | 1.2 (0.4-3.1) | | 5.0 (2.9-8.6) | | 0.7 (0.3-1.6) | |

[a] Data missing in one patient with a malignant neoplasm. [b] Data missing in one patient with T2DM. [c] Data missing in two patients with T2DM. [d] Data missing in one patient with a myocardial infarction. [e] Data missing in two patients with a myocardial infarction. [f] Data missing in one patient with a cerebral infarction. [g] Data missing in five patients with a cerebral infarction. [h] Data missing in five patients with a fracture. [i] Data missing in one patient with a fracture. CI = confidence interval; NC = not calculated; P = P-value; SIR = standardized incidence ratio; T2DM = type 2 diabetes mellitus.

with craniopharyngioma had no increased risk for malignant neoplasms, myocardial infarction, or fractures.

Excess morbidity was similar in patients treated before and after 1987, except for T2DM (SIR 1.8 vs. 5.9; *P*<0.05) and fractures (SIR 2.2 vs. 0.7; *P*<0.05). There was no difference in excess morbidity between Dutch and Swedish patients (Supplementary Table 5.1). To account for survivorship bias, we also evaluated radiotherapy, tumour recurrence, panhypopituitarism, and obesity as risk factors for excess morbidity after the exclusion of patients who died within the first six months after their initial craniopharyngioma treatment (i.e. three patients). This did not significantly affect the results (Supplementary Table 5.2).

## Excess mortality

Excess mortality and risk factors for excess total mortality in patients with craniopharyngioma are shown in Figure 5.1 and Table 5.3, respectively. There were 34 observed

**Table 5.3.** Risk factors for excess total mortality in patients with craniopharyngioma

| Risk factors | Observed | Expected | SMR | 95%CI | *P*-value |
|---|---|---|---|---|---|
| Female | 18 | 3.4 | 5.3 | 3.3-8.4 | <0.05 |
| Male | 16 | 9.0 | 1.8 | 1.1-2.9 | |
| Childhood-onset | 13 | 1.4 | 9.0 | 5.3-15.6 | <0.05 |
| Adult-onset | 21 | 11.0 | 1.9 | 1.2-2.9 | |
| Hydrocephalus | 15 | 1.4 | 10.5 | 6.3-17.4 | <0.05 |
| No hydrocephalus | 19 | 10.5 | 1.8 | 1.2-2.8 | |
| Hypothalamic damage[a] | 16 | 4.3 | 3.7 | 2.3-6.0 | 0.12 |
| No hypothalamic damage | 15 | 6.9 | 2.2 | 1.3-3.6 | |
| Complete resection[b] | 6 | 3.5 | 1.7 | 0.8-3.9 | 0.15 |
| Incomplete resection | 16 | 5.0 | 3.2 | 2.0-5.2 | |
| Radiotherapy | 15 | 4.8 | 3.1 | 1.9-5.2 | 0.53 |
| No radiotherapy | 19 | 7.6 | 2.5 | 1.6-3.9 | |
| Recurrence[c] | 19 | 3.7 | 5.1 | 3.3-8.0 | <0.05 |
| No recurrence | 14 | 8.7 | 1.6 | 1.0-2.7 | |
| Panhypopituitarism[c] | 15 | 3.5 | 4.3 | 2.6-7.1 | <0.05 |
| No panhypopituitarism | 18 | 8.9 | 2.0 | 1.3-3.2 | |
| Obesity[d] | 14 | 4.2 | 3.3 | 2.0-5.6 | 0.08 |
| No obesity | 13 | 7.5 | 1.7 | 1.0-3.0 | |
| Treatment <1987 | 8 | 3.4 | 2.4 | 1.2-4.8 | 0.64 |
| Treatment ≥1987 | 26 | 9.1 | 2.9 | 2.0-4.2 | |

[a]Data missing in three patients who died. [b]Data missing in 12 patients who died. [c]Data missing in one patient who died. [d]Data missing in seven patients who died. CI = confidence interval; SMR = standardized mortality ratio.

deaths in patients with craniopharyngioma compared to 12.4 expected, resulting in a significantly increased SMR for total mortality of 2.7 (95%CI 2.0-3.8). The risk for excess total mortality was significantly higher in females compared to males (SMR 5.3 vs. 1.8; $P<0.05$), patients with childhood- compared to adult-onset craniopharyngioma (SMR 9.0 vs. 1.9; $P<0.05$), patients with compared to without hydrocephalus (SMR 10.5 vs. 1.8; $P<0.05$), patients with compared to without tumour recurrence (SMR 5.1 vs. 1.6; $P<0.05$), and patients with compared to without panhypopituitarism (SMR 4.3 vs. 2.0; $P<0.05$). There was no difference in excess total mortality between patients treated before and after 1987. In addition, excess total mortality was similar in Dutch and Swedish patients (Supplementary Table 5.1). The exclusion of the patients who died within the first six months after their initial craniopharyngioma treatment did not significantly affect the results on risk factors for excess total mortality (Supplementary Table 5.2).

In the analyses on cause-specific mortality, we observed a significantly increased risk for mortality due to circulatory diseases (ICD-10 chapter 9) (SMR 2.3, 95%CI 1.1-4.5) and respiratory diseases (ICD-10 chapter 10) (SMR 6.0, 95%CI 2.5-14.5). The excess risk for mortality due to circulatory diseases was mainly due to cerebrovascular disease. We observed no excess mortality due to malignant neoplasms and ischemic heart disease. The low number of observed deaths precluded the reliable assessment of determinants of cause-specific mortality. Individual causes of death in patients with craniopharyngioma are shown in Supplementary Table 5.3.

## DISCUSSION

In this large hospital-based retrospective cohort study, we investigated excess morbidity and mortality in 224 patients with craniopharyngioma after 3153 person-years of follow-up. We observed patients with craniopharyngioma to be at significantly increased risk for T2DM, cerebral infarction, total mortality, and mortality due to circulatory and respiratory diseases relative to the general population. The excess risk for mortality due to circulatory diseases was mainly due to a high cerebrovascular mortality. We identified female sex, childhood-onset craniopharyngioma, hydrocephalus, hypothalamic damage, incomplete tumour resection, radiotherapy, tumour recurrence, panhypopituitarism, and obesity as significant risk factors for excess morbidity and mortality in a series of univariable analyses.

Similar to our study, some previous studies investigated morbidity and mortality in patients with craniopharyngioma relative to the general population (Table 5.4).[2, 15-19] The results of these studies are in concordance with our findings regarding the significantly increased risk for T2DM, cerebral infarction, total mortality, and mortality due to circulatory and respiratory diseases in patients with craniopharyngioma. The increased risk for

**Table 5.4.** Other studies that investigated excess mortality in patients with craniopharyngioma

| References | Country | Setting | Period | n (%) | Median age at craniopharyngioma dx. (range) (yr.) | Median follow-up (range) yr. | Person-years | SMR for total mortality (95%CI) |
|---|---|---|---|---|---|---|---|---|
| Bulow et al.[15] | Sweden | Hospital-based | 1951-1988 | ♀ 24 (40) ♂ 36 (60) | 28 (3-71) | 13 (0-40) | NA | 5.6 (3.7-8.2) |
| Tomlinson et al.[16] | United Kingdom | Hospital-based | 1992-2000 | ♀/♂ 118 | NA | NA | NA | 9.3 (5.8-14.8) |
| Pereira et al.[17] | The Netherlands | Hospital-based | 1965-2002 | ♀ 30 (55) ♂ 25 (45) | 29 (4-74) | 10 (1-37) | 828 | 2.9 (1.4-5.0) |
| Crowley et al.[18] | Ireland | Hospital-based | 1980-2008 | ♀ 31 (44) ♂ 39 (56) | 28 (0-80) | 8 (1-50) | NA | 8.8 (5.4-13.3) |
| Gaillard et al.[19] | KIMS-database[b] | Hospital-based | 1994-2011 | ♀/♂ 1562 | NA | NA | 8392 | 2.5 (1.9-3.1) |
| Olsson et al.[2] | Sweden | Population-based | 1987-2011 | ♀ 156 (51) ♂ 151 (49) | 35 (0-81)[c] | 9 (0-25)[c] | 2882 | 3.8 (2.9-5.0) |
| Wijnen et al.[a] | The Netherlands and Sweden | Hospital-based | 1987-2014 | ♀ 105 (47) ♂ 119 (43) | 20 (9-42)[d] | 13 (6-21)[d] | 3153 | 2.7 (2.0-3.8) |

[a]Current study. [b]Pfizer International Metabolic Database. [c]Mean (range). [d]Median (interquartile range). ♀ = female; ♂ = male; CI = confidence interval; dx. = diagnosis; n = number; NA = not available; SMR = standardized mortality ratio; yr. = years.

circulatory diseases in patients with craniopharyngioma seems to be mainly due to an adverse metabolic profile associated with hypothalamic damage and hypopituitarism.[14, 21] Hypothalamic damage may result in acquired leptin and insulin resistance, as well as autonomic nervous system dysfunction, which may altogether promote the development of obesity and its associated metabolic derangements.[22] The adverse metabolic profile associated with hypopituitarism may be due to inadequately treated pituitary hormone deficiencies, as well as to currently available hormone replacement regimens that do not appropriately simulate hypothalamic-pituitary physiology.[23-25] The increased risk for respiratory mortality has also been observed in patients with hypopituitarism due to other causes,[4] and is likely to be due to an increased incidence of severe respiratory tract infections. Secondary adrenal insufficiency and glucocorticoid replacement therapy, as well as immune dysfunction associated with other pituitary hormone deficiencies seem to be responsible for an increased infection risk in patients with hypopituitarism.[26] In our study, all patients who died from respiratory diseases suffered from secondary adrenal insufficiency. In these patients, fatal events were probably at least partly due to adrenal crises related to secondary adrenal insufficiency. This is supported by Burman et al., who found that adrenal crises in response to acute stress and intercurrent illness contribute to death in adult patients with hypopituitarism.[27] Patients with craniopharyngioma seem to be at increased risk for mortality compared to patients with hypopituitarism due to other causes.[4] This may be due to craniopharyngioma-specific factors, like a locally aggressive tumour behaviour, a high recurrence rate, severe hypopituitarism, and a high frequency of hypothalamic damage.

We identified female sex, childhood-onset disease, hydrocephalus, tumour recurrence, and panhypopituitarism as the most important risk factors for excess morbidity and mortality in patients with craniopharyngioma in a series of univariable analyses. Although previous studies evaluated only a few potential determinants of excess morbidity and mortality in patients with craniopharyngioma, some of them also observed a significantly increased risk for excess morbidity and mortality associated with female sex, childhood-onset craniopharyngioma, and panhypopituitarism.[2, 15, 17] The reason for the increased morbidity and mortality in female compared to male patients with craniopharyngioma is unknown, but sex-specific factors associated with hypopituitarism and its management are likely to be involved.[4] This is illustrated by studies in patients with hypopituitarism due to various causes that also observed a significantly increased risk for excess mortality associated with female sex.[28] Nielsen et al. suggested that pituitary hormone deficiencies may be underdiagnosed in females compared to males due to the absence of sex-specific diagnostic tests.[29] In their study, they observed a substantially lower prevalence of pituitary hormone deficiencies in female compared to male patients after surgery for non-functioning pituitary adenoma. In addition, Erfurth et al. reported a significantly longer duration of untreated hypopituitarism in female (but not in male)

patients with pituitary tumours (including craniopharyngioma) who died of cerebrovascular disease.[30] Moreover, some studies suggested that sex-specific differences in the pathophysiological states associated with pituitary hormone deficiencies and effects of currently available hormone replacement regimens contribute to the increased morbidity and mortality in female compared to male patients with pituitary disease.[4, 21, 28]

The increased morbidity and mortality in patients with childhood- compared to adult-onset craniopharyngioma may be explained by tumour characteristics. Wijnen et al. reported that patients with childhood-onset disease present significantly more multicystic tumours, as well as tumours associated with hydrocephalus and hypothalamic damage compared to patients with adult-onset disease.[7] Tumour characteristics may also explain the significantly increased risk for excess morbidity and mortality associated with hydrocephalus and tumour recurrence. Large and aggressive craniopharyngiomas that cause hydrocephalus and tend to recur after treatment may induce more tumour- and treatment-related brain damage, thereby increasing the risk for excess morbidity and mortality.

Radiotherapy is as an important risk factor for cerebrovascular disease.[31] Interestingly, we observed an equal excess risk for cerebral infarction in patients treated with and without radiotherapy. This indicates that other factors, like neurosurgery and an adverse metabolic profile associated with hypothalamic damage and hypopituitarism, also contribute to the excess risk for cerebral infarction in patients with craniopharyngioma. Additionally, our study population may be too young and our follow-up duration too short to observe an increased risk for cerebral infarction associated with radiotherapy. Previous studies identified an advanced age and a prolonged follow-up duration after radiotherapy as important risk factors for radiation-induced cerebrovascular disease.[31] This latter explanation may potentially also apply to the absence of an increased risk for myocardial infarction and malignant neoplasms in patients with craniopharyngioma in our study.

Our study has several strengths. We investigated morbidity and mortality in patients with craniopharyngioma relative to the general population. Additionally, we studied a large number of potential risk factors for excess morbidity and mortality. Furthermore, through international collaboration, we could establish a large cohort of both patients with childhood- and adult-onset craniopharyngioma. The international collaboration also enabled us to replicate our findings in two study populations. Despite these strengths, some limitations of our study should be discussed. The (tertiary) hospital-based setting may induce selection bias of patients with more advanced disease. Additionally, we included patients with craniopharyngioma treated before 1987, which increased the size of our study population and thereby the strength of our analyses, but may have also induced a survivorship bias. However, when we analysed this issue, we did not find any survivorship bias, except for T2DM. This indicates that the true excess risk

for T2DM might be even higher than SIR 4.4 (95%CI 2.8-6.8). Another limitation of our study is the use of Swedish general population data to calculate SIRs in Dutch patients with craniopharyngioma. Although the Swedish general population has been reported to be slightly healthier than the Dutch general population, the difference is minimal.[32] An additional limitation of our study is that we defined hypothalamic damage based on data reported in the medical records. Recently, several neuroradiological grading systems for craniopharyngioma-related hypothalamic damage have been developed.[33-36] Mortini et al. validated some of these classification systems regarding their correlation with obesity.[37] Unfortunately, due to the retrospective design of our study, we were unable to use these classification systems. Future studies are needed to validate these grading systems and to investigate their correlation with other symptoms of hypothalamic damage. Furthermore, in our study, data on lifestyle factors and the histological subtype of craniopharyngioma were unavailable. Another limitation of our study is that the cause of death was unknown in seven patients with craniopharyngioma. Although this did not affect the SMR for total mortality, the cause-specific SMRs could have been underestimated. Since many patients with craniopharyngioma suffer from growth hormone deficiency and secondary adrenal insufficiency,[7] and since these conditions are known to be associated with excess circulatory and respiratory mortality,[4] it is tempting to speculate that mortality due to circulatory, as well as respiratory diseases may have been underestimated in our study. In addition, a previous study by Burman et al. has shown that deaths due to adrenal crises related to secondary adrenal insufficiency are probably underestimated in patients with hypopituitarism as well.[27] Moreover, 67 of the 80 Swedish patients with craniopharyngioma enrolled in our study also took part in a previous study on excess morbidity and mortality in patients with craniopharyngioma.[2] This previous population-based study by Olsson et al. was a nationwide study that included 307 patients with craniopharyngioma from Sweden. In this study, excess morbidity and mortality were investigated using registry-provided data only. Since the current study used data derived from the medical records to examine excess morbidity and mortality, the results provided in the present study are more accurate and extensive compared to the previous study by Olsson et al.[2] We were able to study a relatively large number of new risk factors for excess morbidity and mortality. In addition, the follow-up duration in the current study is considerably longer compared to the previous study by Olsson et al. (i.e. median 13 vs. 8 years).[2] Lastly, our results on risk factors for excess morbidity and mortality should be interpreted cautiously because many determinants of excess morbidity and mortality in patients with craniopharyngioma are interrelated (e.g. radiotherapy, hypothalamic damage, panhypopituitarism, and obesity).

In conclusion, we observed patients with craniopharyngioma to be at significantly increased risk for T2DM, cerebral infarction, total mortality, and mortality due to circulatory and respiratory diseases relative to the general population. The excess risk for

mortality due to circulatory diseases was mainly due to a high cerebrovascular mortality. We identified female sex, childhood-onset disease, hydrocephalus, tumour recurrence, and panhypopituitarism as the most important risk factors for excess morbidity and mortality in patients with craniopharyngioma in a series of univariable analyses. Since excess morbidity and mortality in patients with craniophayrngioma is highly dependent on tumour- and treatment-related hypothalamic-pituitary damage, we advocate individualized treatment strategies that aim to preserve hypothalamic-pituitary function and provide optimal endocrine care.

**SUPPLEMENTARY DATA**

**ICD-10 codes for morbidities (ICD-9 codes are shown in parentheses):**

Malignant neoplasms: C00-C97 (140-208)

Type 2 diabetes mellitus: E11 (250)

Myocardial infarction: I21 (410)

Cerebral infarction: I63 (430-434, 436-438)

Fractures: S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T14.2 (800.0-800.3, 801.0-801.3, 802, 803.0-803.3, 804.0-804.3, 805.0-805.7, 806.0-806.7, 807.0-807.6, 808.0-808.5, 808.8-808.9, 809.0-809.1, 810.0-810.1, 812.0-812.5, 813.0-813.5, 814.0-814.1, 815.0-815.1, 816.0-816.1, 817.0-817.1, 818.0-818.1, 819.0-819.1, 820.0-820.3, 820.8-820.9, 821.0-821.3, 822.0-822.1, 823.0-823.3, 824, 825.0-825.3, 826.0-826.1, 827.0-827.1, 828.0-828.1, 829.0-829.1)

**ICD-10 codes for cause-specific mortality (ICD-9 codes are shown in parentheses):**

Malignant neoplasms: C00-C97 (140-208)

Circulatory diseases (chapter 9): I00-I99 (390-459)

- Ischemic heart disease: I20-I25 (410-414)

- Cerebrovascular disease: I60-I69 (430-438)

Respiratory diseases (chapter 10): J00-J99 (460-519)

**Supplementary Table 5.1.** Excess morbidity and mortality in patients with craniopharyngioma according to country of origin

| Morbidity | Observed | Expected | SIR/SMR | 95%CI | *P*-value |
|---|---|---|---|---|---|
| *Malignant neoplasms* | | | | | |
| The Netherlands | 6 | 6.7 | 0.9 | 0.4-2.0 | 1.00 |
| Sweden | 4 | 4.6 | 0.9 | 0.3-2.3 | |
| *T2DM* | | | | | |
| The Netherlands | 12 | 2.6 | 4.7 | 2.7-8.3 | 0.72 |
| Sweden | 8 | 2.0 | 4.0 | 2.0-8.0 | |
| *Myocardial infarction* | | | | | |
| The Netherlands | 5 | 2.8 | 1.8 | 0.7-4.3 | NC |
| Sweden | 2 | 2.0 | NC | NC | |
| *Cerebral infarction* | | | | | |
| The Netherlands | 12 | 2.1 | 5.7 | 3.3-10.1 | 0.39 |
| Sweden | 5 | 1.3 | 3.7 | 1.6-9.0 | |
| *Fractures* | | | | | |
| The Netherlands | 9 | 7.0 | 1.3 | 0.7-2.5 | 0.76 |
| Sweden | 5 | 4.5 | 1.1 | 0.5-2.7 | |
| **Mortality** | | | | | |
| *Total mortality* | | | | | |
| The Netherlands | 24 | 8.1 | 3.0 | 2.0-4.4 | 0.49 |
| Sweden | 10 | 4.4 | 2.3 | 1.2-4.3 | |

CI = confidence interval; NC = not calculated; SIR = standardized incidence ratio; SMR = standardized mortality ratio; T2DM = type 2 diabetes mellitus.

**Supplementary Table 5.2.** Risk factors for excess morbidity and mortality (patients who died ≤6 months after their initial craniopharyngioma treatment excluded)

| Morbidity | Observed | Expected | SIR/SMR | 95%CI | *P*-value |
|---|---|---|---|---|---|
| *Malignant neoplasms* | 10 | 11.3 | 0.9 | 0.5-1.7 | |
| Radiotherapy | 6 | 5.0 | 1.2 | 0.5-2.7 | |
| No radiotherapy | 4 | 6.2 | 0.6 | 0.2-1.7 | 0.32 |
| Recurrence | 4 | 3.8 | 1.1 | 0.4-2.8 | |
| No recurrence | 6 | 7.4 | 0.8 | 0.4-1.8 | 0.61 |
| Panhypopituitarism | 3 | 4.2 | 0.7 | 0.2-2.2 | |
| No panhypopituitarism | 7 | 7.1 | 1.0 | 0.5-2.1 | 0.62 |
| Obesity[a] | 3 | 4.8 | 0.6 | 0.2-1.9 | |
| No obesity | 6 | 5.8 | 1.0 | 0.5-2.3 | 0.46 |
| *T2DM* | 20 | 4.6 | 4.4 | 2.8-6.8 | |
| Radiotherapy | 14 | 2.1 | 6.8 | 4.0-11.5 | |
| No radiotherapy | 6 | 2.5 | 2.4 | 1.1-5.3 | <0.05 |
| Recurrence | 10 | 1.5 | 6.5 | 3.5-12.2 | |
| No recurrence | 10 | 3.0 | 3.3 | 1.8-6.2 | <0.05 |
| Panhypopituitarism | 12 | 1.6 | 7.3 | 4.1-12.8 | |
| No panhypopituitarism | 8 | 2.9 | 2.7 | 1.4-5.5 | <0.05 |
| Obesity | 15 | 1.7 | 8.8 | 5.3-14.7 | |
| No obesity | 5 | 2.6 | 1.9 | 0.8-4.7 | <0.05 |
| *Myocardial infarction* | 6 | 4.8 | 1.3 | 0.6-2.8 | |
| Radiotherapy | 4 | 2.1 | 1.9 | 0.7-5.0 | |
| No radiotherapy | 2 | 2.7 | NC | NC | NC |
| Recurrence[b] | 3 | 1.5 | 2.0 | 0.6-6.1 | |
| No recurrence | 2 | 3.3 | NC | NC | NC |
| Panhypopituitarism | 3 | 1.5 | 2.1 | 0.7-6.4 | |
| No panhypopituitarism | 3 | 3.3 | 0.9 | 0.3-2.8 | 0.29 |
| Obesity | 4 | 1.7 | 2.4 | 0.9-6.3 | |
| No obesity | 2 | 2.9 | NC | NC | NC |
| *Cerebral infarction* | 17 | 3.4 | 5.0 | 3.1-8.0 | |
| Radiotherapy | 7 | 1.4 | 4.9 | 2.3-10.2 | |
| No radiotherapy | 10 | 2.0 | 5.0 | 2.7-9.3 | 0.97 |
| Recurrence[c] | 9 | 1.1 | 8.0 | 4.2-15.3 | |
| No recurrence | 7 | 2.3 | 3.0 | 1.5-6.4 | <0.05 |
| Panhypopituitarism | 7 | 1.0 | 6.9 | 3.3-14.4 | |
| No panhypopituitarism | 10 | 2.4 | 4.1 | 2.2-7.7 | 0.29 |
| Obesity[c] | 7 | 1.2 | 5.6 | 2.7-11.8 | |
| No obesity | 9 | 2.0 | 4.6 | 2.4-8.8 | 0.70 |

**Supplementary Table 5.2.** Risk factors for excess morbidity and mortality (patients who died ≤6 months after their initial craniopharyngioma treatment excluded) (continued)

| Morbidity | Observed | Expected | SIR/SMR | 95%CI | *P*-value |
|---|---|---|---|---|---|
| *Fractures* | 14 | 11.5 | 1.2 | 0.7-2.1 | |
| Radiotherapy | 5 | 5.4 | 0.9 | 0.4-2.2 | 0.34 |
| No radiotherapy | 9 | 6.1 | 1.5 | 0.8-2.8 | |
| Recurrence[d] | 2 | 3.9 | NC | NC | NC |
| No recurrence | 11 | 7.5 | 1.5 | 0.8-2.7 | |
| Panhypopituitarism | 6 | 5.5 | 1.1 | 0.5-2.4 | 0.75 |
| No panhypopituitarism | 8 | 6.0 | 1.3 | 0.7-2.7 | |
| Obesity[d] | 5 | 5.2 | 1.0 | 0.4-2.3 | 0.48 |
| No obesity | 8 | 5.4 | 1.5 | 0.7-2.9 | |
| **Mortality** | | | | | |
| *Total mortality* | 31 | 12.4 | 2.5 | 1.8-3.5 | |
| Radiotherapy | 15 | 4.8 | 3.1 | 1.9-5.2 | 0.27 |
| No radiotherapy | 16 | 7.6 | 2.1 | 1.3-3.4 | |
| Recurrence[e] | 19 | 3.7 | 5.1 | 3.3-8.0 | <0.05 |
| No recurrence | 11 | 8.7 | 1.3 | 0.7-2.3 | |
| Panhypopituitarism[e] | 15 | 3.5 | 4.3 | 2.6-7.1 | <0.05 |
| No panhypopituitarism | 15 | 8.9 | 1.7 | 1.1-2.8 | |
| Obesity[f] | 14 | 4.2 | 3.3 | 2.0-5.6 | 0.08 |
| No obesity | 13 | 7.5 | 1.7 | 1.0-3.0 | |

[a]Data missing in one patient with a malignant neoplasm. [b]Data missing in one patient with a myocardial infarction. [c]Data missing in one patient with a cerebral infarction. [d]Data missing in one patient with a fracture. [e]Data missing in one patient who died. [f]Data missing in four patients who died. CI = confidence interval; NC = not calculated; SIR = standardized incidence ratio; SMR = standardized mortality ratio; T2DM = type 2 diabetes mellitus.

**Supplementary Table 5.3.** Individual causes of death in patients with craniopharyngioma

| Sex | Age at craniopharyngioma dx. (yr.) | Cause of death | Age at death (yr.) |
|---|---|---|---|
| Female | 2 | Cerebral herniation (due to recurrent craniopharyngioma) | 4 |
| Female | 2 | Cerebral herniation (due to recurrent craniopharyngioma) | 7 |
| Male | 5 | Compression of vital brain structures (due to recurrent craniopharyngioma) | 28 |
| Female | 7 | Pneumonia | 8 |
| Male | 8 | Haemorrhagic pancreatitis | 12 |
| Female | 9 | Compression of vital brain structures (due to recurrent craniopharyngioma) | 18 |
| Female | 9 | Unknown | 29 |
| Female | 9 | Cerebral haemorrhage | 42 |
| Female | 12 | Cerebral infarction | 38 |
| Male | 14 | Sepsis (in a patient with extensive primary craniopharyngioma growth) | 25 |
| Male | 14 | Pneumonia | 28 |
| Male | 14 | Myocardial infarction | 43 |
| Male | 17 | Unknown | 28 |
| Male | 35 | Meningitis | 36 |
| Female | 35 | Unknown | 57 |
| Female | 36 | Non-infective gastro-enteritis (in a patient with extensive recurrent craniopharyngioma growth) | 53 |
| Female | 40 | Cerebral infarction | 48 |
| Female | 41 | Pneumonia | 50 |
| Female | 41 | Myocardial infarction | 73 |
| Male | 45 | Cerebral infarction | 67 |
| Female | 51 | Obesity hypoventilation syndrome | 55 |
| Female | 54 | Unknown | 59 |
| Male | 54 | Lung cancer | 78 |
| Male | 57 | Unknown | 65 |
| Male | 61 | Myocardial infarction | 72 |
| Male | 62 | Prostate cancer | 73 |
| Male | 63 | Compression of vital brain structures (due to primary craniopharyngioma) | 63 |
| Female | 64 | Pancreatic cancer | 81 |
| Male | 67 | Myocardial infarction | 67 |
| Female | 69 | Breast cancer | 72 |
| Female | 69 | Unknown | 72 |
| Female | 72 | Unknown | 76 |
| Male | 77 | Pneumonia | 80 |
| Male | 79 | Liver failure | 92 |

dx. = diagnosis; yr. = years.

## REFERENCES

1.  Muller HL. Craniopharyngioma. *Endocr Rev* 2014 er20131115.
2.  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. *J Clin Endocrinol Metab* 2015 **100** 467-474.
3.  Nielsen EH, Feldt-Rasmussen U, Poulsgaard L, Kristensen LO, Astrup J, Jorgensen JO, Bjerre P, Andersen M, Andersen C, Jorgensen J, Lindholm J & Laurberg P. Incidence of craniopharyngioma in Denmark (n = 189) and estimated world incidence of craniopharyngioma in children and adults. *J Neurooncol* 2011 **104** 755-763.
4.  Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, Bates AS & Stewart PM. Mortality in patients with pituitary disease. *Endocr Rev* 2010 **31** 301-342.
5.  Lopez-Serna R, Gomez-Amador JL, Barges-Coll J, Nathal-Vera E, Revuelta-Gutierrez R, Alonso-Vanegas M, Ramos-Peek M & Portocarrero-Ortiz L. Treatment of craniopharyngioma in adults: systematic analysis of a 25-year experience. *Arch Med Res* 2012 **43** 347-355.
6.  Du C, Feng CY, Yuan XR, Liu Q, Peng ZF, Jiang XJ, Li XJ, Xiao GL, Li YF & Xiong T. Microsurgical Management of Craniopharyngiomas via a Unilateral Subfrontal Approach: A Retrospective Study of 177 Continuous Cases. *World Neurosurg* 2016 **90** 454-468.
7.  Wijnen M, van den Heuvel-Eibrink MM, Janssen JA, Catsman-Berrevoets CE, Michiels EM, van Veelen-Vincent MC, Dallenga AH, van den Berge JH, van Rij CM, Van der Lely AJ & Neggers SJ. Very long-term sequelae of craniopharyngioma. *Eur J Endocrinol* 2017.
8.  Sughrue ME, Yang I, Kane AJ, Fang S, Clark AJ, Aranda D, Barani IJ & Parsa AT. Endocrinologic, neurologic, and visual morbidity after treatment for craniopharyngioma. *J Neurooncol* 2011 **101** 463-476.
9.  Gautier A, Godbout A, Grosheny C, Tejedor I, Coudert M, Courtillot C, Jublanc C, De Kerdanet M, Poirier JY, Riffaud L, Sainte-Rose C, Van Effenterre R, Brassier G, Bonnet F, Touraine P & Craniopharyngioma Study G. Markers of recurrence and long-term morbidity in craniopharyngioma: a systematic analysis of 171 patients. *J Clin Endocrinol Metab* 2012 **97** 1258-1267.
10. Tan TS, Patel L, Gopal-Kothandapani JS, Ehtisham S, Ikazoboh EC, Hayward R, Aquilina K, Skae M, Thorp N, Pizer B, Didi M, Mallucci C, Blair JC, Gaze MN, Kamaly-Asl I, Spoudeas H & Clayton PE. The neuroendocrine sequelae of paediatric craniopharyngioma: a 40 year meta-data analysis of 185 cases from three UK centres. *Eur J Endocrinol* 2017.
11. Shi X, Zhou Z, Wu B, Zhang Y, Qian H, Sun Y, Yang Y, Yu Z, Tang Z & Lu S. Outcome of Radical Surgical Resection for Craniopharyngioma with Hypothalamic Preservation: A Single-Center, Retrospective Study of 1054 Patients. *World Neurosurg* 2017.
12. Yuen KC, Koltowska-Haggstrom M, Cook DM, Fox JL, Jonsson PJ, Geffner ME & Abs R. Primary treatment regimen and diabetes insipidus as predictors of health outcomes in adults with childhood-onset craniopharyngioma. *J Clin Endocrinol Metab* 2014 **99** 1227-1235.
13. 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** 1029-1038.
14. Wijnen M, Olsson DS, van den Heuvel-Eibrink MM, Hammarstrand C, Janssen J, Van der Lely AJ, Johannsson G & Neggers S. The metabolic syndrome and its components in 178 patients treated for craniopharyngioma after 16 years of follow-up. *Eur J Endocrinol* 2017.

15. Bulow B, Attewell R, Hagmar L, Malmstrom P, Nordstrom CH & Erfurth EM. Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumor recurrence. *J Clin Endocrinol Metab* 1998 **83** 3897-3904.

16. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC & Stewart PM. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet* 2001 **357** 425-431.

17. Pereira AM, Schmid EM, Schutte PJ, Voormolen JH, Biermasz NR, van Thiel SW, Corssmit EP, Smit JW, Roelfsema F & Romijn JA. High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. *Clin Endocrinol (Oxf)* 2005 **62** 197-204.

18. Crowley RK, Hamnvik OP, O'Sullivan EP, Behan LA, Smith D, Agha A & Thompson CJ. Morbidity and mortality in patients with craniopharyngioma after surgery. *Clin Endocrinol (Oxf)* 2010 **73** 516-521.

19. Gaillard RC, Mattsson AF, Akerblad AC, Bengtsson BA, Cara J, Feldt-Rasmussen U, Koltowska-Haggstrom M, Monson JP, Saller B, Wilton P & Abs R. Overall and cause-specific mortality in GH-deficient adults on GH replacement. *Eur J Endocrinol* 2012 **166** 1069-1077.

20. Altman DG & Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003 **326** 219.

21. Erfurth EM, Holmer H & Fjalldal SB. Mortality and morbidity in adult craniopharyngioma. *Pituitary* 2013 **16** 46-55.

22. 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** 1774-1797.

23. Higham CE, Johannsson G & Shalet SM. Hypopituitarism. *Lancet* 2016 **388** 2403-2415.

24. Olsson DS, Trimpou P, Hallen T, Bryngelsson IL, Andersson E, Skoglund T, Bengtsson BA, Johannsson G & Nilsson AG. Life expectancy in patients with pituitary adenoma receiving growth hormone replacement. *Eur J Endocrinol* 2017 **176** 67-75.

25. Hammarstrand C, Ragnarsson O, Hallen T, Andersson E, Skoglund T, Nilsson AG, Johannsson G & Olsson DS. Higher Glucocorticoid Replacement Doses Are Associated with Increased Mortality in Patients with Pituitary Adenoma. *Eur J Endocrinol* 2017.

26. Mukherjee A, Helbert M, Davis J & Shalet S. Immune function in hypopituitarism: time to reconsider? *Clin Endocrinol (Oxf)* 2010 **73** 425-431.

27. Burman P, Mattsson AF, Johannsson G, Hoybye C, Holmer H, Dahlqvist P, Berinder K, Engstrom BE, Ekman B, Erfurth EM, Svensson J, Wahlberg J & Karlsson FA. Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. *J Clin Endocrinol Metab* 2013 **98** 1466-1475.

28. Nielsen EH, Lindholm J & Laurberg P. Excess mortality in women with pituitary disease: a meta-analysis. *Clin Endocrinol (Oxf)* 2007 **67** 693-697.

29. Nielsen EH, Lindholm J, Laurberg P, Bjerre P, Christiansen JS, Hagen C, Juul S, Jorgensen J, Kruse A & Stochholm K. Nonfunctioning pituitary adenoma: incidence, causes of death and quality of life in relation to pituitary function. *Pituitary* 2007 **10** 67-73.

30. Erfurth EM, Bulow B, Svahn-Tapper G, Norrving B, Odh K, Mikoczy Z, Bjork J & Hagmar L. Risk factors for cerebrovascular deaths in patients operated and irradiated for pituitary tumors. *J Clin Endocrinol Metab* 2002 **87** 4892-4899.

31. Plummer C, Henderson RD, O'Sullivan JD & Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. *Stroke* 2011 **42** 2410-2418.

32.  Mackenbach JP, McKee M & (Eds.). *Successes and Failures of Health Policy in Europe: Four Decades of Diverging Trends and Converging Challenges*. Buckingham: Open University Press, 2013.

33.  Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, Zerah M, Bezerra M, Renier D, Pierre-Kahn A & Sainte-Rose C. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. *J Neurosurg* 2007 **106** 3-12.

34.  Van Gompel JJ, Nippoldt TB, Higgins DM & Meyer FB. Magnetic resonance imaging-graded hypothalamic compression in surgically treated adult craniopharyngiomas determining postoperative obesity. *Neurosurg Focus* 2010 **28** E3.

35.  Muller HL, Gebhardt U, Teske C, Faldum A, Zwiener I, Warmuth-Metz M, Pietsch T, Pohl F, Sorensen N, Calaminus G & Study Committee of K. Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. *Eur J Endocrinol* 2011 **165** 17-24.

36.  Mallucci C, Pizer B, Blair J, Didi M, Doss A, Upadrasta S, Newman W, Avula S & Pettorini B. Management of craniopharyngioma: the Liverpool experience following the introduction of the CCLG guidelines. Introducing a new risk assessment grading system. *Childs Nerv Syst* 2012 **28** 1181-1192.

37.  Mortini P, Gagliardi F, Bailo M, Spina A, Parlangeli A, Falini A & Losa M. Magnetic resonance imaging as predictor of functional outcome in craniopharyngiomas. *Endocrine* 2016 **51** 148-162.

# Chapter 6

## The metabolic syndrome and its components in 178 patients treated For craniopharyngioma after 16 years of follow-up

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## ABSTRACT

**Objective:** Patients with craniopharyngioma are at increased risk for cardio- and cerebrovascular mortality. The metabolic syndrome (MetS) is an important cardiometabolic risk factor, but barely studied in patients with craniopharyngioma. We aimed to investigate the prevalence of and risk factors for the MetS and its components in patients with craniopharyngioma.

**Design:** Cross-sectional study with retrospective data.

**Methods:** We studied the prevalence of and risk factors for the MetS and its components in 110 Dutch (median age 47 years, range 18-92) and 68 Swedish (median age 50 years, range 20-81) patients with craniopharyngioma with ≥3 years of follow-up (90 females [51%]; 83 patients with childhood-onset craniopharyngioma [47%]; median follow-up after craniopharyngioma diagnosis 16 years [range 3-62]). In Dutch patients aged 30-70 years and Swedish patients aged 45-69 years, we examined the prevalence of the MetS and its components relative to the general population.

**Results:** Sixty-nine of 149 patients with complete data demonstrated the MetS (46%). Prevalence of the MetS was significantly higher in patients with craniopharyngioma compared with the general population (40% vs. 26% [*P*<0.05] for Dutch patients; 52% vs. 15% [*P*<0.05] for Swedish patients). Multivariable logistic regression analysis identified visual impairment as a borderline significant predictor of the MetS (OR 2.54, 95%CI 0.95-6.81; *P*=0.06) after adjustment for glucocorticoid replacement therapy and follow-up duration. Age, female sex, tumour location, radiological hypothalamic damage, [90]Yttrium brachytherapy, glucocorticoid replacement therapy, and follow-up duration significantly predicted components of the MetS.

**Conclusions:** Patients with craniopharyngioma are at increased risk for the MetS, especially patients with visual impairment.

## INTRODUCTION

Craniopharyngiomas are (supra)sellar epithelial tumours that often contain calcifications and fluid-filled cysts. Despite their benign histology, they are associated with significant morbidity due to both tumour and treatment.[1] Craniopharyngiomas affect children and adults and are predominantly diagnosed between 5-9 and 40-44 years of age.[2] They are usually treated with neurosurgical excision with or without postoperative radiotherapy. Other treatment options include the intracystic appliance of beta-emitting isotopes or chemotherapeutic substances, as well as stereotactic radiosurgery.[1] Patients with craniopharyngioma are at increased risk for premature mortality.[3-6] The most important cause of premature mortality in patients with craniopharyngioma is cardio- and cerebrovascular disease, with a reported standardized mortality ratio between 3.2-19.4.[4-6] The increased risk for cardio- and cerebrovascular mortality in patients with craniopharyngioma is poorly understood but likely to be multifactorial. Tumour- and treatment-related damage of critical neurovascular structures (e.g. hypothalamus, pituitary, optic nerves, and carotid arteries), as well as their associated morbidities with currently available management options (e.g. present hormone replacement regimens for hypopituitarism) may be involved.

Studies in the general population identified the metabolic syndrome (MetS) as an important risk factor for cardio- and cerebrovascular disease, as well as type 2 diabetes mellitus.[7] The MetS, which was conceptualized by Reaven in 1988,[8] has been associated with a two-fold increased risk for cardio- and cerebrovascular disease and a five-fold increased risk for type 2 diabetes mellitus.[7] During the last two decades, several definitions of the MetS have been proposed.[9-14] All these definitions include obesity, insulin resistance, dyslipidaemia, and elevated blood pressure as their main components. To date, only a few studies assessed the MetS and its components in patients with craniopharyngioma.[15-20] Small study populations that mainly consist of children, a lack of comparison with the general population, and the evaluation of only a few potential risk factors for the MetS and its components are major limitations of these studies.

The objectives of our study were to determine the prevalence of and risk factors for the MetS and its components in patients with craniopharyngioma. In a subset of patients, we examined the prevalence of the MetS and its components in relation to the general population.

## SUBJECTS AND METHODS

### Study population

Patients treated for craniopharyngioma at the Erasmus University Medical Centre (Rotterdam, the Netherlands) and the Sahlgrenska University Hospital (Gothenburg, Sweden) were eligible for participation in this cross-sectional study with retrospective data if they were ≥18 years of age at their last follow-up visit, had ≥3 years of follow-up after craniopharyngioma diagnosis, and presented data on ≥1 component of the MetS. A computer-based search in the medical records identified 225 patients with craniopharyngioma of whom 178 were eligible (110 Dutch and 68 Swedish patients). Craniopharyngiomas were diagnosed <18 years of age (i.e. childhood-onset) in 83 patients (47%) and ≥18 years of age (i.e. adult-onset) in 95 patients (53%). All patients gave their informed consent and were included in the study.

In a subset of patients, we examined the prevalence of the MetS, its components, and type 2 diabetes mellitus in relation to the general population. This includes Dutch patients aged 30-70 years (*n*=73) and Swedish patients aged 45-69 years (*n*=29). Data from the Dutch general population were reported in the "Nederland de Maat Genomen" (NL de Maat) study;[21] data from the Swedish general population in the "Life conditions, Stress and Health" (LSH) study.[22] In the "NL de Maat" study, 2059 females and 1806 males from the Dutch general population, aged 30-70 years, were assessed for cardio- and cerebrovascular disease risk factors between 2009-2010.[21] The "LSH" study included 505 females and 502 males from the Swedish general population, aged 45-69 years, who were evaluated for cardio- and cerebrovascular disease risk factors between 2003-2004.[22] The local institutional review board of the Erasmus University Medical Centre and the regional ethical review board in Gothenburg, Sweden, approved this study.

### Data collection

Data on baseline characteristics, tumour characteristics, craniopharyngioma treatment, recurrence, and long-term health outcome were collected from the medical records. Craniopharyngioma location, hydrocephalus, and radiological hypothalamic damage were studied as tumour characteristics. Location was classified as intrasellar, suprasellar, and both intra-/suprasellar. Radiological hypothalamic damage was defined as tumour- and/or treatment-related injury to the hypothalamus and/or third ventricle as visualized on neuroimaging. Neurosurgery, radiotherapy, and [90]Yttrium brachytherapy were studied as craniopharyngioma treatment modalities. Recurrence was defined as reappearance or re-growth of the craniopharyngioma after prior treatment. The MetS and parameters reflecting its components (i.e. body mass index, fasting glucose, triglycerides, high-density lipoprotein [HDL] cholesterol, systolic and diastolic blood pressure), presence of and treatment for diabetes mellitus, dyslipidaemia, and hypertension,

glycated haemoglobin (HbA1c), cardio- and cerebrovascular morbidity, presence of and treatment for hypopituitarism, visual impairment, and current treatment for epilepsy and psychiatric illness were studied as conditions reflecting long-term health outcome. The MetS was defined according to the Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (Table 6.1).[14] According to this definition, patients are classified as obese if waist circumference is greater than population- and country-specific definitions or if body mass index is >30 kg/m$^2$. Because data on waist circumference were unavailable in our patients, we classified patients as obese by body mass index only. Pituitary hormone deficiencies were diagnosed by formal pituitary function testing in all patients. Growth hormone replacement therapy (GHRT) was started based on clinical guidelines and shared decision making. Sex steroid replacement therapy was discontinued in females when a physiological menopausal age was reached (i.e. approximately 51 years). Visual impairment was defined as a decreased visual acuity after correction for refraction disorders and/or as the presence of a visual field defect.

**Table 6.1.** Definition of the MetS[14]

| At least three of the following five criteria: |
| --- |
| Body mass index >30 kg/m$^2$ |
| Fasting glucose ≥5.6 mmol/L or drug treatment for increased glucose |
| Triglycerides ≥1.7 mmol/L or drug treatment for elevated triglycerides |
| HDL cholesterol <1.0 mmol/L in males and <1.3 mmol/L in females or drug treatment for reduced HDL cholesterol |
| Blood pressure ≥130/85 mmHg or drug treatment for hypertension |

MetS = Metabolic syndrome.

## Statistical analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS 24, Chicago, IL, USA). Evaluations were based on the number of patients with available data. Continuous and categorical variables were compared using Student's *t*-tests and Chi-squared tests, respectively. Non-parametric equivalent tests were used when assumptions were not met. Prevalence of the MetS, its components, and type 2 diabetes mellitus were compared between patients with craniopharyngioma and the general population using one-sample proportion tests. Logistic regression analyses were performed to identify risk factors for the MetS and its components. Age, sex, age group at craniopharyngioma diagnosis, tumour location, hydrocephalus, radiological hypothalamic damage, radiotherapy, [90]Yttrium brachytherapy, craniopharyngioma recurrence, panhypopituitarism, treatment of growth hormone deficiency (GHD), hypogonadotropic

hypogonadism, secondary adrenal insufficiency, secondary hypothyroidism, and diabetes insipidus, as well as visual impairment and treatment for epilepsy and psychiatric illness were evaluated as potential risk factors. Variables statistically significant in univariable regression (i.e. a *P*-value <0.05 [two-tailed]) were further evaluated by multivariable regression. All multivariable regression analyses were adjusted for follow-up duration.

## RESULTS

### Patient characteristics

We evaluated 178 patients with craniopharyngioma (90 females [51%]) (Table 6.2). Median follow-up after craniopharyngioma diagnosis was 16 years (range 3-62). Median age at last follow-up assessment was 47 years (range 18-92) (i.e. median 47 years [range 18-92] in Dutch patients, and median 50 years [range 20-81] in Swedish patients). Patient characteristics were similar in females and males, except for secondary hypothyroidism (88% vs. 97%; *P*<0.05). GHRT was used by 117 patients with GHD (79%). Thirty-five (30%) of these patients used GHRT during childhood. Sex steroid replacement therapy was used by 122 patients with hypogonadotropic hypogonadism (95% of males and premenopausal females). All premenopausal females on sex steroid replacement therapy used regular oral oestrogen-progestin replacement regimens. Three males did not use sex steroid replacement therapy due to prostate cancer. All patients with secondary adrenal insufficiency, secondary hypothyroidism, and diabetes insipidus were adequately treated with hormone replacement therapy. Glucocorticoid replacement therapy was used by 145 patients (82%). The median daily hydrocortisone equivalent dose in these patients was 20 milligrams (range 5-50). Antiepileptic drugs were used by 15 patients (8%); psychiatric drugs (i.e. antipsychotics, antidepressants, or benzodiazepines) by 24 patients (14%). One patient was known with type 1 diabetes mellitus; another patient had gestational diabetes. These two patients were excluded from the analyses on the MetS and its components.

Patient characteristics in Dutch compared with Swedish patients with craniopharyngioma, patients with childhood- compared with adult-onset craniopharyngioma, patients with treated compared with untreated GHD, and patients with obesity compared to patients without obesity are shown in Supplementary Table 6.1.

### The MetS and its components

In our study, 69 of 149 patients with complete data demonstrated the MetS (46%) (Table 6.3). Twenty patients (29%) had three components of the MetS, 30 patients (43%) four components, and 14 patients (20%) five components. In five patients with the MetS (7%) the exact number of components was unknown. Obesity was present in 84 patients

**Table 6.2.** Patient characteristics

| | All craniopharyngiomas (*n*=178) | Females (*n*=90) | Males (*n*=88) |
|---|---|---|---|
| **Baseline characteristics** | | | |
| Age at diagnosis (years)[a] | 23 (0-79) | 23 (4-73) | 24 (0-79) |
| Childhood-onset (*n* [%]) | 83 (47) | 40 (44) | 43 (49) |
| Adult-onset (*n* [%]) | 95 (53) | 50 (56) | 45 (51) |
| Follow-up since diagnosis (years)[a] | 16 (3-62) | 16 (3-62) | 18 (3-48) |
| Age at last follow-up assessment (years)[a] | 47 (18-92) | 48 (18-82) | 47 (18-92) |
| **Tumour characteristics** | | | |
| Location (*n* [%]) | | | |
| Intrasellar | 4 (2) | 1 (1) | 3 (4) |
| Suprasellar | 67 (40) | 34 (41) | 33 (40) |
| Intra-/suprasellar | 95 (57) | 49 (58) | 46 (52) |
| Hydrocephalus (*n* [%]) | 47 (27) | 26 (29) | 21 (24) |
| Radiological hypothalamic damage (*n* [%]) | 65 (39) | 31 (37) | 34 (42) |
| **Craniopharyngioma treatment** | | | |
| Neurosurgery (*n* [%]) | 165 (93) | 84 (93) | 81 (92) |
| Radiotherapy (*n* [%]) | 85 (48) | 43 (48) | 42 (48) |
| [90]Yttrium brachytherapy (*n* [%]) | 29 (16) | 16 (18) | 13 (15) |
| Recurrence (*n* [%]) | 70 (40) | 36 (40) | 34 (40) |
| **Long-term health outcome** | | | |
| Pituitary hormone deficiencies (*n* [%]) | | | |
| GH | 148 (85)[b] | 73 (82) | 75 (88) |
| FSH/LH | 155 (88)[c] | 76 (84) | 79 (91) |
| ACTH | 145 (82)[d] | 69 (77) | 76 (86) |
| TSH | 163 (92)[d] | 78 (88) | 85 (97) |
| ADH | 111 (62)[d] | 55 (61) | 56 (64) |
| Panhypopituitarism | 93 (53) | 46 (51) | 47 (54) |
| Visual impairment (*n* [%]) | 126 (78) | 63 (77) | 63 (80) |
| Body mass index (kg/m$^2$)[a] | 30.1 (16.9-59.5) | 30.4 (20.3-59.5) | 30.1 (16.9-49.1) |
| Treatment for epilepsy (*n* [%]) | 15 (8) | 5 (6) | 10 (11) |
| Treatment for psychiatric illness (*n* [%]) | 24 (14) | 11 (13) | 13 (15) |

[a]Median (range). [b]GHRT was used by 117 patients with GHD (79%). [c]Sex steroid replacement therapy was used by 122 patients with hypogonadotropic hypogonadism (95% of males and premenopausal females). [d]All patients were adequately treated with hormone replacement therapy. ACTH = Adrenocorticotropic hormone; ADH = Antidiuretic hormone; FSH/LH = Follicle stimulating hormone/luteinizing hormone; GH = Growth hormone; GHD = Growth hormone deficiency; GHRT = Growth hormone replacement therapy; kg/m$^2$ = Kilograms per square metre; *n* = Number; TSH = Thyroid stimulating hormone.

(52%). Increased fasting glucose affected 57 patients (37%); elevated triglycerides 80 patients (54%). Reduced HDL cholesterol was found in 65 patients (46%); and elevated

**Table 6.3.** The MetS, its components, type 2 diabetes mellitus, and cardio- and cerebrovascular morbidity in patients with craniopharyngioma

| | Patients with craniopharyngioma | Comparison with general population | | | | | | Dutch vs. Sweden | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | | Dutch patients[c] | General population[21] | P-value | Swedish patients[d] | General population[22] | P-value | | |
| **MetS and its components** | | | | | | | | | |
| MetS | 69/149 (46%) | 22/55 (40%) | 29% | <0.05 | 15/29 (52%) | 15% | <0.05 | 48% vs. 44% | 0.61 |
| Obesity | 84/162 (52%) | 34/63 (54%) | 13% | <0.05 | 14/28 (50%) | 33% | <0.05 | 54% vs. 49% | 0.48 |
| Increased fasting glucose | 57/156 (37%) | 13/61 (21%) | NA | NA | 15/29 (52%) | NA | NA | 29% vs. 47% | <0.05 |
| Elevated triglycerides | 80/149 (54%) | 27/56 (48%) | NA | NA | 18/29 (62%) | 25% | <0.05 | 54% vs. 54% | 0.97 |
| Reduced HDL cholesterol | 65/141 (46%) | 18/51 (35%) | 6% | <0.05 | 16/29 (55%) | 11% | <0.05 | 47% vs. 45% | 0.74 |
| Elevated blood pressure | 96/172 (56%) | 44/69 (64%) | 31% | <0.05 | 15/29 (52%) | 27% | <0.05 | 62% vs. 47% | 0.06 |
| **Type 2 diabetes mellitus and cardio- and cerebrovascular morbidity** | | | | | | | | | |
| Type 2 diabetes mellitus | 24/178 (14%) | 8/73 (11%) | 5% | <0.05 | 5/29 (17%) | 6% | <0.05 | 15% vs. 12% | 0.60 |
| HbA1c (mmol/mol)[a,b] | 34 (23-80) | 36 (22-69) | NA | NA | 36 (29-77) | NA | NA | 36 vs. 33 | 0.29 |
| Myocardial infarction | 6/178 (3%) | 4/73 (6%) | NA | NA | 0/29 (0%) | NA | NA | 6% vs. 0% | 0.08 |
| Cerebrovascular accident | 15/178 (8%) | 4/73 (6%) | NA | NA | 1/29 (3%) | NA | NA | 9% vs. 7% | 0.69 |

[a]Median (range). [b]Data available in 118 patients. [c]Subset of Dutch patients aged 30-70 years. Dutch = Dutch patients with craniopharyngioma; HbA1c = Glycated haemoglobin; HDL = High-density lipoprotein; MetS = Metabolic syndrome; NA = Not available; Swedish = Swedish patients with craniopharyngioma. [d]Subset of Swedish patients aged 45-69 years.

blood pressure in 96 patients (56%). In the subset of patients who were compared with the general population (i.e. Dutch patients aged 30-70 years and Swedish patients aged 45-69 years), prevalence of the MetS was significantly higher in patients with craniopharyngioma (40% vs. 29% [*P*<0.05] for Dutch patients; 52% vs. 15% [*P*<0.05] for Swedish patients). Prevalence of obesity, reduced HDL cholesterol, and elevated blood pressure were also significantly higher in Dutch and Swedish patients with craniopharyngioma compared with the general population. Prevalence of elevated triglycerides could only be compared with the general population in Swedish patients with craniopharyngioma. In this subgroup, prevalence of elevated triglycerides was significantly higher in patients with craniopharyngioma (Table 6.3).

Prevalence of the MetS and its components were similar in Dutch and Swedish patients with craniopharyngioma, except for increased fasting glucose, which was significantly more common in Swedish compared with Dutch patients (47% vs. 29%; *P*<0.05) (Table 6.3). Female patients had a significantly higher prevalence of reduced HDL cholesterol (58% vs. 35%; *P*<0.05) and elevated blood pressure (64% vs. 47%; *P*<0.05) compared with male patients. Elevated blood pressure was significantly more common in patients with adult- compared with childhood-onset craniopharyngioma (64% vs. 46%; *P*<0.05). There were no significant differences in the MetS and its components between patients with treated and untreated GHD (Table 6.4).

**Table 6.4.** The MetS, its components, type 2 diabetes mellitus, and cardio- and cerebrovascular morbidity in subgroups

| | ♀ vs. ♂ | *P*-value | CO vs. AO | *P*-value | GHRT vs. non-GHRT | *P*-value |
|---|---|---|---|---|---|---|
| **MetS and its components** | | | | | | |
| MetS | 54% vs. 40% | 0.09 | 48% vs. 45% | 0.71 | 43% vs. 57% | 0.24 |
| Obesity | 56% vs. 48% | 0.35 | 59% vs. 45% | 0.08 | 57% vs. 43% | 0.19 |
| Increased fasting glucose | 32% vs. 41% | 0.26 | 33% vs. 39% | 0.44 | 33% vs. 40% | 0.49 |
| Elevated triglycerides | 59% vs. 49% | 0.20 | 47% vs. 60% | 0.12 | 51% vs. 58% | 0.51 |
| Reduced HDL cholesterol | 58% vs. 35% | <0.05 | 51% vs. 42% | 0.28 | 47% vs. 38% | 0.47 |
| Elevated blood pressure | 64% vs. 47% | <0.05 | 46% vs. 64% | <0.05 | 52% vs. 67% | 0.16 |
| | | | | | | |
| **Type 2 diabetes mellitus and cardio- and cerebrovascular morbidity** | | | | | | |
| Type 2 diabetes mellitus | 14% vs. 13% | 0.70 | 11% vs. 16% | 0.34 | 10% vs. 23% | 0.08 |
| HbA1c (mmol/mol)[a,b] | 35 vs. 34 | 0.74 | 33 vs. 36 | 0.15 | 34 vs. 37 | 0.72 |
| Myocardial infarction | 4% vs. 2% | 0.68 | 1% vs. 5% | 0.22 | 2% vs. 7% | 0.19 |
| Cerebrovascular accident | 9% vs. 8% | 0.82 | 7% vs. 10% | 0.59 | 6% vs. 16% | 0.13 |

[a]Median (range). [b]Data available in 118 patients. ♀ = Female; ♂ = Male; AO = Adult-onset craniopharyngioma; CO = Childhood-onset craniopharyngioma; GHRT = Treated growth hormone deficiency; HbA1c = Glycated haemoglobin; HDL = High-density lipoprotein; MetS = Metabolic syndrome; Non-GHRT = Untreated growth hormone deficiency.

## Risk factors for the MetS and its components in patients with craniopharyngioma

Results of the univariable and multivariable logistic regression analyses on risk factors for the MetS are shown in Table 6.5. Glucocorticoid replacement therapy (OR 3.27, 95%CI 1.22-8.74; $P$<0.05) and visual impairment (OR 2.63, 95%CI 1.11-6.24; $P$<0.05) were identified as significant risk factors for the MetS in the univariable analyses. In the multivariable analysis, visual impairment was borderline significantly associated with the MetS (OR 2.54, 95%CI 0.95-6.81; $P$=0.06) after adjustment for glucocorticoid replacement therapy and follow-up duration. Radiological hypothalamic damage was identified as a significant risk factor for obesity (OR 9.86, 95%CI 1.59-61.1; $P$<0.05) after adjustment for age, [90]Yttrium brachytherapy, craniopharyngioma recurrence, vasopressin treatment, panhypopituitarism, treatment for psychiatric illness, and follow-up duration. A pro-

**Table 6.5.** Risk factors for the MetS in patients with craniopharyngioma

| Parameters | Univariable analysis | | Multivariable analysis[c,d] | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | *P*-value | Odds ratio (95% CI) | *P*-value |
| Age (in years) | 1.01 (0.99-1.03) | 0.22 | | |
| Female sex | 1.69 (0.89-3.23) | 0.11 | | |
| Childhood-onset disease | 1.10 (0.58-2.09) | 0.78 | | |
| Tumour location[a] | | | | |
| Suprasellar | 1.15 (0.15-8.71) | 0.89 | | |
| Intra-/suprasellar | 0.70 (0.09-5.20) | 0.72 | | |
| Hydrocephalus | 1.43 (0.69-2.98) | 0.34 | | |
| Radiological hypothalamic damage | 1.49 (0.76-2.94) | 0.25 | | |
| Radiotherapy | 1.29 (0.68-2.46) | 0.43 | | |
| [90]Yttrium brachytherapy | 2.61 (0.99-6.89) | 0.05 | | |
| Craniopharyngioma recurrence | 1.44 (0.74-2.77) | 0.28 | | |
| Panhypopituitarism | 1.43 (0.75-2.73) | 0.28 | | |
| Treatment of GHD | 0.58 (0.24-1.45) | 0.24 | | |
| Sex steroid replacement[b] | 2.57 (0.26-25.5) | 0.42 | | |
| Glucocorticoid replacement | 3.27 (1.22-8.74) | <0.05 | 2.32 (0.80-6.73) | 0.12 |
| Thyroid hormone replacement | 2.72 (0.53-13.9) | 0.23 | | |
| Vasopressin treatment | 1.27 (0.65-2.48) | 0.49 | | |
| Visual impairment | 2.63 (1.11-6.24) | <0.05 | 2.54 (0.95-6.81) | 0.06 |
| Treatment for epilepsy | 0.82 (0.25-2.69) | 0.74 | | |
| Treatment for psychiatric illness | 0.46 (0.18-1.19) | 0.11 | | |

[a]Compared with intrasellar. [b]In males and premenopausal females only. [c]Analysis adjusted for follow-up duration. [d]Cox & Snell $R^2$=0.06; model $\chi^2$=6.87; $P$=0.08. CI = Confidence interval; GHD = Growth hormone deficiency; MetS = Metabolic syndrome.

longed follow-up duration significantly decreased the risk for increased fasting glucose (OR 0.93, 95%CI 0.88-0.97; *P*<0.05). Intrasellar tumour location significantly protected for elevated triglycerides (OR 0.43, 95%CI 0.21-0.88; *P*<0.05) after adjustment for age and follow-up duration. Female sex (OR 3.29, 95%CI 1.35-8.01; *P*<0.05), [90]Yttrium brachytherapy (OR 7.87, 95%CI 1.58-39.2; *P*<0.05), and glucocorticoid replacement therapy (OR 4.80, 95%CI 1.12-20.6; *P*<0.05) were identified as significant risk factors for reduced HDL cholesterol after adjustment for hydrocephalus, craniopharyngioma recurrence, and follow-up duration. Age (OR 1.06, 95%CI 1.02-1.10; *P*<0.05) significantly predicted elevated blood pressure after adjustment for female sex, childhood-onset craniopharyngioma and follow-up duration.

Since visual impairment was identified as a borderline significant predictor for the MetS (i.e. our primary study outcome), we compared baseline, tumour, and treatment characteristics, as well as long-term health outcome between patients with and without visual impairment (Table 6.6). Craniopharyngioma treatment with [90]Yttrium brachytherapy (21% vs. 6%; *P*<0.05) and tumour recurrence (47% vs. 17%; *P*<0.05) were significantly more frequent in patients with compared to without visual impairment.

**Type 2 diabetes mellitus and cardio- and cerebrovascular morbidity**

In our study, 24 patients (14%) suffered from type 2 diabetes mellitus (Table 6.3). Eleven of them received insulin treatment. In the subset of patients who were compared with the general population, prevalence of type 2 diabetes mellitus was significantly higher in patients with craniopharyngioma (11% vs. 6% [*P*<0.05] for Dutch patients; 17% vs. 6% [*P*<0.05] for Swedish patients). In our study, six patients with craniopharyngioma (3%) experienced a myocardial infarction, and 15 patients (8%) suffered from a cerebrovascular accident. One patient with childhood-onset craniopharyngioma had a myocardial infarction at the age of 38 years. In patients with adult-onset craniopharyngioma, the median age at myocardial infarction was 53 years (range 32-73 years). Cerebrovascular accidents affected six patients with childhood-onset craniopharyngioma at a median age of 31 years (range 19-38). The median age of cerebrovascular accident in patients with adult-onset craniopharyngioma was 64 years (range 35-77). Prevalence of type 2 diabetes mellitus, myocardial infarction, and cerebrovascular accident, as well as HbA1c levels were similar in Dutch and Swedish patients with craniopharyngioma (Table 6.3), as well as in females and males, patients with childhood- and adult-onset craniopharyngioma, and patients with treated and untreated GHD (Table 6.4).

**Table 6.6.** Patients with compared to without visual impairment

| | Visual impairment (*n*=126) | No visual impairment (*n*=35) | *P*-value |
|---|---|---|---|
| **Baseline characteristics** | | | |
| ♀ (*n* [%]) | 63 (50) | 19 (54) | 0.65 |
| ♂ (n [%]) | 63 (50) | 16 (46) | |
| Age at diagnosis (years)[a] | 26 (0-79) | 17 (5-61) | 0.26 |
| Childhood-onset (*n* [%]) | 59 (47) | 16 (46) | 0.91 |
| Adult-onset (*n* [%]) | 67 (53) | 19 (54) | |
| Follow-up since diagnosis (years)[a] | 16 (3-62) | 17 (6-39) | 0.49 |
| Age at last follow-up assessment (years)[a] | 48 (18-92) | 47 (18-81) | 0.71 |
| **Tumour characteristics** | | | |
| Location (*n* [%]) | | | 0.88 |
| Intrasellar | 3 (3) | 1 (3) | 1.00 |
| Suprasellar | 49 (41) | 12 (36) | 0.62 |
| Intra-/suprasellar | 67 (56) | 20 (61) | 0.66 |
| Hydrocephalus (*n* [%]) | 38 (30) | 6 (18) | 0.14 |
| Radiological hypothalamic damage (*n* [%]) | 46 (39) | 13 (41) | 0.84 |
| **Craniopharyngioma treatment** | | | |
| Neurosurgery (*n* [%]) | 120 (95) | 31 (87) | 0.23 |
| Radiotherapy (*n* [%]) | 64 (51) | 14 (40) | 0.26 |
| [90]Yttrium brachytherapy (*n* [%]) | 27 (21) | 1 (6) | <0.05 |
| Recurrence (*n* [%]) | 59 (47) | 6 (17) | <0.05 |
| **Long-term health outcome** | | | |
| Pituitary hormone deficiencies (*n* [%]) | | | |
| GH | 107 (87) | 28 (80) | 0.30 |
| FSH/LH | 109 (87) | 30 (86) | 0.78 |
| ACTH | 105 (83) | 26 (74) | 0.22 |
| TSH | 117 (94) | 30 (86) | 0.16 |
| ADH | 82 (65) | 22 (63) | 0.81 |
| Panhypopituitarism | 68 (54) | 19 (54) | 0.99 |
| Body mass index (kg/m$^2$)[a] | 30.4 (16.9-59.5) | 31.0 (24.6-48.7) | 0.47 |
| Treatment for epilepsy (*n* [%]) | 12 (10) | 1 (3) | 0.30 |
| Treatment for psychiatric illness (*n* [%]) | 15 (12) | 6 (17) | 0.41 |
| **MetS and its components** | | | |
| MetS (*n* [%]) | 56 (52) | 9 (29) | <0.05 |
| Obesity (*n* [%]) | 60 (53) | 19 (54) | 0.86 |
| Increased fasting glucose (*n* [%]) | 47 (41) | 8 (26) | 0.12 |
| Elevated triglycerides (*n* [%]) | 60 (56) | 13 (45) | 0.30 |
| Reduced HDL cholesterol (*n* [%]) | 52 (51) | 10 (35) | 0.13 |
| Elevated blood pressure (*n* [%]) | 69 (56) | 20 (57) | 0.91 |

[a]Median (range). ♀ = Female; ♂ = Male; ACTH = Adrenocorticotropic hormone; ADH = Antidiuretic hormone; FSH/LH = Follicle stimulating hormone/luteinizing hormone; GH = Growth hormone; GHD = Growth hormone deficiency; GHRT = Growth hormone replacement therapy; HDL = High-density lipoprotein; kg/m$^2$ = Kilograms per square metre; MetS = Metabolic syndrome; *n* = Number; TSH = Thyroid stimulating hormone.

## DISCUSSION

We performed the largest study that investigated the MetS and its components in patients with craniopharyngioma to date. After a median follow-up duration of 16 years, almost half of the patients with craniopharyngioma demonstrated the MetS. Accordingly, in a subset of Dutch and Swedish patients who were compared with the general population, we found that the MetS was significantly more prevalent than expected. Using multivariable logistic regression analyses adjusted for follow-up duration, we identified visual impairment, radiological hypothalamic damage, tumour location, female sex, [90]Yttrium brachytherapy, glucocorticoid replacement therapy, and age as significant risk factors for the MetS and its components.

In our study, prevalence of the MetS in patients with craniopharyngioma was 46%. Other studies that investigated the MetS in patients with craniopharyngioma observed a prevalence between 8-67% (Table 6.7).[15-20] This wide variation in prevalence may be related to heterogeneity in study populations and difference in definitions used to classify patients as exhibiting the MetS. In the subset of Dutch and Swedish patients with craniopharyngioma who were compared with the general population, we observed a significantly higher prevalence of the MetS than expected. This is in concordance with three small other studies that also compared the prevalence of the MetS between patients with craniopharyngioma and control subjects.[15, 17, 18] Studies that investigated the MetS in patients with hypopituitarism due to various causes (including craniopharyngioma) did not observe any significant difference in the prevalence of the MetS between patients with craniopharyngioma and patients with hypopituitarism due to other causes, at least in patients with untreated GHD.[18, 23, 24] Profka et al. observed that the beneficial metabolic effects of GHRT were less pronounced in patients with craniopharyngioma compared with patients with hypopituitarism due to non-functioning pituitary adenoma. In their study, prevalence of the MetS was significantly higher in patients with craniopharyngioma compared with patients with non-functioning pituitary adenoma after five years of GHRT (37% vs. 5%; $P<0.05$).[18]

The increased susceptibility for the MetS and its components in patients with craniopharyngioma is likely to be multifactorial. Tumour- and treatment-related damage of important brain structures, as well as their associated morbidities with currently available management options may altogether adversely affect metabolic function. This makes it challenging to evaluate risk factors for the MetS and its components. Nevertheless, we assessed patients with craniopharyngioma for predictors of an adverse metabolic state. Using multivariable logistic regression analyses adjusted for follow-up duration, we identified visual impairment as a borderline significant risk factor for the MetS. Radiological hypothalamic damage significantly increased the risk for obesity. A prolonged follow-up duration significantly decreased the risk for increased fasting glucose.

**Table 6.7.** Studies investigating the MetS in patients with craniopharyngioma

| References | n | Median age at craniopharyngioma dx (range) (yr.) | Median age (range) (yr.) | Median follow-up (range) (yr.) | Pituitary hormone deficiencies | Definition MetS | Prevalence MetS[a] | Subgroup results |
|---|---|---|---|---|---|---|---|---|
| Pereira et al.[16] | ♀ 30 ♂ 25 | 29 (4-74) | 49 (6-76) | 10 (1-37) | GH 89%[b] FSH/LH 88%[c] ACTH 88% TSH 84% ADH 53% Panhyp 89% | NCEP | 47% | ♀ vs. ♂ 57% vs. 24% (P<0.05) |
| Holmer et al.[15] | ♀ 20 ♂ 22 | 12 (3-22) | 28 (17-57) | 20 (4-40) | GH 86%[d] FSH/LH 88%[e] ACTH 86% TSH 93% ADH 83% Panhyp 76% | IDF | 26% vs. 7% (P<0.05) | TGTV vs. non-TGTV 40% vs. 6% (P<0.05) |
| Simoneau-Roy et al.[17] | ♀ 8 ♂ 7 | NA | 15 ± 4[f] | 5 ± 3[f] | GH 53%[g] FSH/LH 33%[h] ACTH 93% TSH 93% ADH 93% Panhyp NA | Modified NCEP and WHO criteria | 67% vs. 20% (P<0.05) | NA |
| Sahakitrungruang et al.[19] | ♀ 5 ♂ 7 | NA | 14 (8-18) | 2 (1-11) | GH 100%[i] FSH/LH 33%[e] ACTH 83% TSH NA ADH NA Panhyp NA | Modified NCEP and WHO criteria | 42% vs. 8% (P=0.16) | NA |
| Profka et al.[18] | ♀ 7 ♂ 12 | 42 ± 13[f] | 47 ± 13[f] | 5 ± 0[f] | GH 100%[j] FSH/LH 74%[e] ACTH 90% TSH 95% ADH 79% Panhyp 63% | NCEP | 37% vs. 5% (P<0.05)[k] | GHRT vs. non-GHRT 37% vs. 31%[l] |

**Table 6.7.** Studies investigating the MetS in patients with craniopharyngioma (continued)

| References | n | Median age at craniopharyngioma dx (range) (yr.) | Median age (range) (yr.) | Median follow-up (range) (yr.) | Pituitary hormone deficiencies | Definition MetS | Prevalence MetS[a] | Subgroup results |
|---|---|---|---|---|---|---|---|---|
| Ferraù et al.[20] | ♀ 12 ♂ 12 | CO 15[m] AO 9 | 38 ± 15[f] | 16 ± 9[f] | GH 96%[n] FSH/LH 96%[e] ACTH 88% TSH 96% ADH 63% Panhyp NA | IDF | 8% | NA |
| Wijnen et al.[o] | ♀ 90 ♂ 88 | 23 (0-79) | 47 (18-92) | 16 (3-62) | GH 85%[p] FSH/LH 88%[q] ACTH 82% TSH 92% ADH 62% Panhyp 53% | Joint Interim Statement | Dutch 46% vs. 29% ($P<0.05$)[r] Swedish 52% vs. 15% ($P<0.05$)[s] | ♀ vs. ♂ 54% vs. 40% ($P=0.09$) CO vs. AO 48% vs. 45% ($P=0.71$) GHRT vs. non-GHRT 43% vs. 57% ($P=0.24$) |

[a]Compared with control subjects. [b]Majority of patients with GHD received no GHRT (exact number of patients not mentioned). [c]Number of patients receiving sex steroid replacement therapy not mentioned. [d]95% of patients with GHD received GHRT. [e]All patients with hypogonadotropic hypogonadism received sex steroid replacement therapy. [f]Mean ± standard deviation. [g]GHD not formally tested; only (pre)pubertal patients with growth failure received GHRT. [h]Not mentioned how many patients exhibited hypogonadotropic hypogonadism; 33% of all patients received sex steroid replacement therapy. [i]No patients with GHD received GHRT. [j]All patients with GHD received GHRT. [k]Compared with patients with non-functioning pituitary adenoma. [l]Prevalence of the MetS after five years of GHRT compared with baseline before the start of GHRT. [m]Childhood-onset defined as ≤18 years at craniopharyngioma diagnosis. [n]70% of patients with GHD received GHRT. [o]Present study. [p]79% of patients with GHD received GHRT. [q]95% of patients with hypogonadotropic hypogonadism received sex steroid replacement therapy. [r]Subset of Dutch patients with craniopharyngioma aged 30-70 years compared with the general population. [s]Subset of Swedish patients with craniopharyngioma aged 45-69 years compared with the general population. ♀ = Female; ♂ = Male; ACTH = Adrenocorticotropic hormone; ADH = Antidiuretic hormone; AO = Adult-onset craniopharyngioma; CO = Childhood-onset craniopharyngioma; dx = Diagnosis; FSH/LH = Follicle stimulating hormone/luteinizing hormone; GH = Growth hormone; GHD = Growth hormone deficiency; GHRT = Growth hormone replacement therapy; IDF = International Diabetes Federation; MetS = Metabolic syndrome; n = Number; NA = Not available; NCEP = National Cholesterol Education Program; Panhyp = Panhypopituitarism; TGTV = Tumour growth into third ventricle; TSH = Thyroid stimulating hormone; WHO = World Health Organization; yr. = years.

Intrasellar tumour location significantly protected for elevated triglycerides. Female sex, [90]Yttrium brachytherapy, and glucocorticoid replacement therapy were identified as significant risk factors for reduced HDL cholesterol. Age significantly predicted elevated blood pressure. The increased risk for the MetS associated with visual impairment may be due to a negative effect of visual impairment on the ability to participate in physical activity. This is illustrated by studies that observed a significantly lower level of physical activity in patients with craniopharyngioma compared with age-, sex-, and body mass index-matched control subjects.[25, 26] A lower level of physical activity has been associated with an increased risk for the MetS in the general population.[27] Differences in tumour characteristics between patients with and without visual impairment may also contribute to the increased risk for the MetS in patients with visual impairment. We found a significantly higher rate of craniopharyngioma recurrence and subsequent treatment with [90]Yttrium brachytherapy in patients with compared to without visual impairment. Craniopharyngioma recurrence and additional treatment may exacerbate tumour- and treatment-related brain damage, thereby increasing the risk for the MetS and its components.

The increased risk for obesity associated with radiological hypothalamic damage may be due to acquired leptin and insulin resistance, as well as autonomic nervous system dysfunction. These factors may adversely affect food intake and energy expenditure, thereby promoting obesity.[28] An increased risk for obesity in patients with craniopharyngioma associated with hypothalamic damage has also been observed in other studies.[29-32] We observed an increased risk for reduced HDL cholesterol associated with female sex. This may be due to currently used oestrogen-progestin replacement regimens that do not fully simulate the physiological menstrual cycle.[33] This is illustrated by a recent study that observed an improved cardiovascular risk profile in premature ovarian insufficient females treated with a more physiological transdermal/transvaginal oestrogen-progestin replacement regimen compared with a regular oral oestrogen-progestin replacement regimen.[34] In our study, all premenopausal females with hypogonadotropic hypogonadism used a regular oral oestrogen-progestin replacement regimen. The increased risk for reduced HDL cholesterol associated with glucocorticoid replacement therapy may be due to currently available glucocorticoid replacement regimens that contain relatively high glucocorticoid doses and are administered in patterns that do not fully simulate the physiological circadian cortisol rhythm in terms of serum level and pulsatility.[35]

Some limitations of our study should be considered. Data on waist circumference were unavailable. This may have led to an underestimation of the prevalence of the MetS and obesity, because those patients with an elevated waist circumference but body mass index ≤30 kg/m$^2$ were misclassified as non-obese. However, we anticipate that this misclassification is small, since several studies advocated that a body mass index of >30

kg/m$^2$ may be used to diagnose obesity as a component of the MetS instead of elevated waist circumference.[14, 36, 37] Moreover, a recent study by Gierach et al. reported a high and significant correlation between body mass index and waist circumference in patients with the MetS ($R$=0.78; $P$<0.01).[38] The "NL de Maat" study and "LSH" study, which were used for the comparisons with the general population, classified participants as obese by waist circumference.[21, 22] Otherwise, there were no substantial differences in the criteria used to define the MetS and its components between our study and the "NL de Maat" study and "LSH" study. Unfortunately, both the "NL de Maat" study and "LSH" study did not report data on increased fasting glucose. Therefore, we were unable to study the prevalence of increased fasting glucose in patients with craniopharygioma relative to the general population. Another limitation of our study is that we were unable to investigate the prevalence of the MetS relative to the general population after adjustment for obesity. Interestingly, when analysing our data, the prevalence of the MetS seems to be lower than the prevalence of obesity in patients with craniopharyngioma, while in the Dutch general population the prevalence of the MetS seems to be higher than the prevalence of obesity. Since visceral adipose tissue-induced insulin resistance is postulated to be the principal factor resulting in the MetS and its components,[7] this indicates that one may expect an even higher prevalence of the MetS in patients with craniopharyngioma. Future studies should clarify this issue. Other limitations of our study include the unavailability of data on ethnicity, lifestyle factors, histological subtype of craniopharyngioma (i.e. adamantinomatous or papillary), and body composition measured by dual-energy X-ray absorptiometry (DXA). Body composition measured by DXA has been shown to be a better predictor for cardio- and cerebrovascular morbidity than body composition measured by anthropometry.[39, 40]

In conclusion, we observed a high prevalence of the MetS and its components in patients with craniopharyngioma. In a subset of Dutch and Swedish patients with craniopharyngioma who were compared with the general population, we found that the MetS was significantly more prevalent than expected. Using multivariable logistic regression analyses adjusted for follow-up duration, we identified visual impairment, radiological hypothalamic damage, tumour location, female sex, [90]Yttrium brachytherapy, glucocorticoid replacement therapy, and age as significant risk factors for the MetS and its components in patients with craniopharyngioma.

**Supplementary Table 6.1.** Patient characteristics according to country, age group at craniopharyngioma diagnosis, treatment of growth hormone replacement therapy, and obesity

| | Dutch (n=110) | Swedish (n=68) | P-value | Childhood (n=83) | Adult (n=95) | P-value | GHRT (n=117) | Non-GHRT (n=31) | P-value | Obese (n=84) | Non-obese (n=79) | P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Baseline characteristics** | | | | | | | | | | | | |
| ♀ (n [%]) | 61 (56) | 29 (43) | 0.10 | 40 (48) | 50 (53) | 0.56 | 55 (47) | 18 (58) | 0.27 | 45 (54) | 37 (47) | 0.39 |
| ♂ (n [%]) | 49 (45) | 39 (57) | | 43 (52) | 45 (47) | | 62 (53) | 13 (42) | | 39 (46) | 42 (53) | |
| Age at diagnosis (years)[a] | 21 (0-79) | 31 (6-68) | 0.31 | 10 (0-17) | 41 (18-79) | <0.05 | 16 (0-57) | 42 (4-73) | <0.05 | 16 (3-62) | 29 (0-79) | 0.06 |
| Childhood-onset (n [%]) | 51 (46) | 32 (47) | 0.93 | | | | 64 (55) | 11 (36) | 0.06 | 47 (56) | 33 (42) | 0.07 |
| Adult-onset (n [%]) | 59 (54) | 36 (53) | | | | | 53 (45) | 20 (65) | | 37 (44) | 46 (58) | |
| Follow-up since diagnosis (years)[a] | 18 (3-62) | 15 (3-31) | <0.05 | 20 (3-62) | 14 (3-35) | <0.05 | 18 (3-62) | 22 (5-36) | 0.50 | 19 (3-62) | 16 (3-53) | 0.37 |
| Age at last follow-up assessment (years)[a] | 47 (18-92) | 50 (20-81) | 0.41 | 32 (18-70) | 57 (25-92) | <0.05 | 42 (18-78) | 57 (18-82) | <0.05 | 43 (18-81) | 50 (18-92) | <0.05 |
| **Tumour characteristics** | | | | | | | | | | | | |
| Location (n [%]) | | | <0.05 | | | 0.23 | | | 0.20 | | | 0.47 |
| Intrasellar | 3 (3) | 1 (2) | 1.00 | 3 (4) | 1 (1) | 0.33 | 1 (1) | 0 (0) | 1.00 | 1 (1) | 3 (4) | 0.34 |
| Suprasellar | 33 (31) | 34 (56) | <0.05 | 26 (35) | 41 (45) | 0.18 | 48 (44) | 8 (28) | 0.11 | 34 (43) | 27 (38) | 0.58 |
| Intra-/suprasellar | 69 (66) | 26 (43) | <0.05 | 46 (61) | 49 (54) | 0.33 | 60 (55) | 21 (72) | 0.09 | 45 (56) | 41 (58) | 0.85 |
| Hydrocephalus (n [%]) | 35 (32) | 12 (18) | <0.05 | 31 (38) | 16 (17) | <0.05 | 32 (28) | 12 (40) | 0.19 | 27 (33) | 16 (21) | 0.09 |
| Radiological hypothalamic damage (n [%]) | 50 (50) | 15 (23) | <0.05 | 34 (45) | 31 (34) | 0.18 | 44 (40) | 13 (45) | 0.61 | 38 (49) | 22 (29) | <0.05 |
| **Craniopharyngioma treatment** | | | | | | | | | | | | |
| Neurosurgery (n [%]) | 99 (90) | 66 (97) | 0.14 | 80 (96) | 85 (90) | 0.08 | 111 (95) | 27 (87) | 0.22 | 79 (94) | 74 (94) | 1.00 |
| Radiotherapy (n [%]) | 50 (46) | 35 (52) | 0.44 | 51 (61) | 34 (36) | <0.05 | 61 (52) | 11 (36) | 0.10 | 48 (57) | 34 (43) | 0.07 |
| $^{90}$Yttrium brachytherapy (n [%]) | 24 (22) | 5 (7) | <0.05 | 15 (18) | 14 (15) | 0.55 | 15 (13) | 8 (26) | 0.10 | 18 (21) | 7 (9) | <0.05 |
| Recurrence (n [%]) | 47 (44) | 23 (34) | 0.18 | 37 (46) | 33 (35) | 0.16 | 50 (43) | 11 (37) | 0.52 | 42 (51) | 26 (33) | <0.05 |

**Supplementary Table 6.1.** Patient characteristics according to country, age group at craniopharyngioma diagnosis, treatment of growth hormone replacement therapy, and obesity (continued)

| | Dutch (n=110) | Swedish (n=68) | P-value | Childhood (n=83) | Adult (n=95) | P-value | GHRT (n=117) | Non-GHRT (n=31) | P-value | Obese (n=84) | Non-obese (n=79) | P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Long-term health outcome** | | | | | | | | | | | | |
| Pituitary hormone deficiencies (n [%]) | | | | | | | | | | | | |
| GH | 90 (85) | 58 (85) | 0.94 | 75 (94) | 73 (78) | <0.05 | 117 (100) | 31 (100) | 1.00 | 76 (91) | 66 (85) | 0.26 |
| FSH/LH | 102 (94) | 53 (78) | <0.05 | 72 (88) | 83 (87) | 0.93 | 109 (93) | 29 (94) | 1.00 | 76 (91) | 69 (87) | 0.52 |
| ACTH | 91 (83) | 54 (79) | 0.58 | 69 (83) | 76 (80) | 0.59 | 102 (87) | 24 (77) | 0.25 | 73 (87) | 62 (79) | 0.15 |
| TSH | 99 (91) | 64 (94) | 0.43 | 79 (95) | 84 (89) | 0.15 | 114 (98) | 28 (90) | 0.06 | 80 (95) | 72 (91) | 0.30 |
| ADH | 61 (56) | 50 (74) | <0.05 | 65 (78) | 46 (48) | <0.05 | 87 (74) | 14 (45) | <0.05 | 61 (73) | 46 (58) | 0.05 |
| Panhypopituitarism | 53 (49) | 40 (59) | 0.19 | 55 (67) | 38 (40) | <0.05 | 80 (68) | 12 (39) | <0.05 | 53 (63) | 37 (47) | <0.05 |
| Visual impairment (n [%]) | 72 (77) | 54 (79) | 0.76 | 59 (79) | 67 (78) | 0.91 | 87 (80) | 20 (77) | 0.74 | 60 (76) | 55 (78) | 0.83 |
| Body mass index (kg/m$^2$)[a] | 30 (17-59) | 30 (22-46) | 0.65 | 31 (17-58) | 30 (20-59) | 0.10 | 31 (17-58) | 27 (23-59) | 0.06 | 34 (30-59) | 27 (17-29) | <0.05 |
| Treatment for epilepsy (n [%]) | 6 (6) | 9 (13) | 0.07 | 11 (13) | 4 (4) | <0.05 | 9 (8) | 3 (10) | 0.72 | 5 (6) | 8 (10) | 0.33 |
| Treatment for psychiatric illness (n [%]) | 7 (7) | 17 (25) | <0.05 | 8 (10) | 16 (17) | 0.16 | 15 (13) | 2 (7) | 0.53 | 7 (8) | 16 (21) | <0.05 |

[a]Median (range). ♀ = Female; ♂ = Male; ACTH = Adrenocorticotropic hormone; ADH = Antidiuretic hormone; Adult = Patients with adult-onset craniopharyngioma; Childhood = Patients with childhood-onset craniopharyngioma; Dutch = Dutch patients with craniopharyngioma; FSH/LH = Follicle stimulating hormone/luteinizing hormone; GH = Growth hormone; GHRT = Patients with treated growth hormone deficiency; kg/m$^2$ = Kilograms per square metre; n = Number; Non-GHRT = Patients with untreated growth hormone deficiency; Non-obese = Non-obese patients with craniopharyngioma; Obese = Obese patients with craniopharyngioma; Swedish = Swedish patients with craniopharyngioma; TSH = Thyroid stimulating hormone.

## REFERENCES

1.  Muller HL. Craniopharyngioma. *Endocr Rev* 2014 er20131115.
2.  Nielsen EH, Feldt-Rasmussen U, Poulsgaard L, Kristensen LO, Astrup J, Jorgensen JO, Bjerre P, Andersen M, Andersen C, Jorgensen J, Lindholm J & Laurberg P. Incidence of craniopharyngioma in Denmark (n = 189) and estimated world incidence of craniopharyngioma in children and adults. *J Neurooncol* 2011 **104** 755-763.
3.  Wijnen M, van den Heuvel-Eibrink MM, Janssen JA, Catsman-Berrevoets CE, Michiels EM, van Veelen-Vincent MC, Dallenga AH, van den Berge JH, van Rij CM, Van der Lely AJ & Neggers SJ. Very long-term sequelae of craniopharyngioma. *Eur J Endocrinol* 2017.
4.  Bulow B, Attewell R, Hagmar L, Malmstrom P, Nordstrom CH & Erfurth EM. Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumor recurrence. *J Clin Endocrinol Metab* 1998 **83** 3897-3904.
5.  Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC & Stewart PM. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet* 2001 **357** 425-431.
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. *J Clin Endocrinol Metab* 2015 **100** 467-474.
7.  Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H & Eckel RH. The metabolic syndrome. *Endocr Rev* 2008 **29** 777-822.
8.  Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988 **37** 1595-1607.
9.  Alberti KG & Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998 **15** 539-553.
10. Balkau B & Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet Med* 1999 **16** 442-443.
11. Expert Panel on Detection E & Treatment of High Blood Cholesterol in A. Executive Summary of The 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). *JAMA* 2001 **285** 2486-2497.
12. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr., Spertus JA, Costa F, American Heart A, National Heart L & Blood I. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005 **112** 2735-2752.
13. Alberti KG, Zimmet P & Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006 **23** 469-480.
14. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC, Jr., International Diabetes Federation Task Force on E, Prevention, Hational Heart L, Blood I, American Heart A, World Heart F, International Atherosclerosis S & International Association for the Study of O. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009 **120** 1640-1645.

15. Holmer H, Ekman B, Bjork J, Nordstom CH, Popovic V, Siversson A & Erfurth EM. Hypothalamic involvement predicts cardiovascular risk in adults with childhood onset craniopharyngioma on long-term GH therapy. *Eur J Endocrinol* 2009 **161** 671-679.

16. Pereira AM, Schmid EM, Schutte PJ, Voormolen JH, Biermasz NR, van Thiel SW, Corssmit EP, Smit JW, Roelfsema F & Romijn JA. High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. *Clin Endocrinol (Oxf)* 2005 **62** 197-204.

17. 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** 364-370.

18. Profka E, Giavoli C, Bergamaschi S, Ferrante E, Malchiodi E, Sala E, Verrua E, Rodari G, Filopanti M, Beck-Peccoz P & Spada A. Analysis of short- and long-term metabolic effects of growth hormone replacement therapy in adult patients with craniopharyngioma and non-functioning pituitary adenoma. *J Endocrinol Invest* 2015 **38** 413-420.

19. Sahakitrungruang T, Klomchan T, Supornsilchai V & Wacharasindhu S. Obesity, metabolic syndrome, and insulin dynamics in children after craniopharyngioma surgery. *Eur J Pediatr* 2011 **170** 763-769.

20. Ferrau F, Spagnolo F, Cotta OR, Cannavo L, Alibrandi A, Russo GT, Aversa T, Trimarchi F & Cannavo S. Visceral adiposity index as an indicator of cardiometabolic risk in patients treated for craniopharyngioma. *Endocrine* 2016.

21. Blokstra A, Vissink P, Venmans LMAJ, Holleman P, van der Schouw YT, Smit HA & Verschuren WMM. [Measuring the Netherlands. A monitoring study of risk factors in the general population, 2009-2010]. pp 1-29, 2011.

22. Hollman G & Kristenson M. The prevalence of the metabolic syndrome and its risk factors in a middle-aged Swedish population--mainly a function of overweight? *Eur J Cardiovasc Nurs* 2008 **7** 21-26.

23. Attanasio AF, Mo D, Erfurth EM, Tan M, Ho KY, Kleinberg D, Zimmermann AG, Chanson P & International Hypopituitary Control Complications Study Advisory B. Prevalence of metabolic syndrome in adult hypopituitary growth hormone (GH)-deficient patients before and after GH replacement. *J Clin Endocrinol Metab* 2010 **95** 74-81.

24. Verhelst J, Mattsson AF, Luger A, Thunander M, Goth MI, Koltowska-Haggstrom M & Abs R. Prevalence and characteristics of the metabolic syndrome in 2479 hypopituitary patients with adult-onset GH deficiency before GH replacement: a KIMS analysis. *Eur J Endocrinol* 2011 **165** 881-889.

25. 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** 5227-5231.

26. Piguel X, Abraham P, Bouhours-Nouet N, Gatelais F, Dufresne S, Rouleau S & Coutant R. Impaired aerobic exercise adaptation in children and adolescents with craniopharyngioma is associated with hypothalamic involvement. *Eur J Endocrinol* 2012 **166** 215-222.

27. He D, Xi B, Xue J, Huai P, Zhang M & Li J. Association between leisure time physical activity and metabolic syndrome: a meta-analysis of prospective cohort studies. *Endocrine* 2014 **46** 231-240.

28. 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** 1774-1797.

29. Muller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, Korinthenberg R, Bettendorf M, Kuhl J, Gutjahr P, Sorensen N & Calaminus G. Obesity after childhood craniopharyngioma--German multicenter study on pre-operative risk factors and quality of life. *Klin Padiatr* 2001 **213** 244-249.

30. Muller HL, Gebhardt U, Etavard-Gorris N, Korenke E, Warmuth-Metz M, Kolb R, Sorensen N & Calaminus G. Prognosis and sequela in patients with childhood craniopharyngioma -- results of HIT-ENDO and update on KRANIOPHARYNGEOM 2000. *Klin Padiatr* 2004 **216** 343-348.

31. Mortini P, Gagliardi F, Bailo M, Spina A, Parlangeli A, Falini A & Losa M. Magnetic resonance imaging as predictor of functional outcome in craniopharyngiomas. *Endocrine* 2016 **51** 148-162.

32. Wijnen M, Olsson DS, van den Heuvel-Eibrink MM, Wallenius V, Janssen J, Delhanty PJ, van der Lely AJ, Johannsson G & Neggers S. Efficacy and safety of bariatric surgery for craniopharyngioma-related hypothalamic obesity-A matched case-control study with two years of follow-up. *Int J Obes (Lond)* 2016.

33. Sullivan SD, Sarrel PM & Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. *Fertil Steril* 2016 **106** 1588-1599.

34. Langrish JP, Mills NL, Bath LE, Warner P, Webb DJ, Kelnar CJ, Critchley HO, Newby DE & Wallace WH. Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure. *Hypertension* 2009 **53** 805-811.

35. Johannsson G & Ragnarsson O. Cardiovascular and metabolic impact of glucocorticoid replacement therapy. *Front Horm Res* 2014 **43** 33-44.

36. Ridker PM, Buring JE, Cook NR & Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 2003 **107** 391-397.

37. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM & Shepherd J. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 2003 **108** 414-419.

38. Gierach M, Gierach J, Ewertowska M, Arndt A & Junik R. Correlation between Body Mass Index and Waist Circumference in Patients with Metabolic Syndrome. *ISRN Endocrinol* 2014 **2014** 514589.

39. Blijdorp K, van den Heuvel-Eibrink MM, Pieters R, Boot AM, Delhanty PJ, van der Lely AJ & Neggers SJ. Obesity is underestimated using body mass index and waist-hip ratio in long-term adult survivors of childhood cancer. *PLoS One* 2012 **7** e43269.

40. Demmer DL, Beilin LJ, Hands B, Burrows S, Cox KL, Pennell CE, Lye SJ, Mountain JA & Mori TA. Dual Energy X-Ray Absorptiometry Compared with Anthropometry in Relation to Cardio-Metabolic Risk Factors in a Young Adult Population: Is the 'Gold Standard' Tarnished? *PLoS One* 2016 **11** e0162164.

# Chapter 7

## Efficacy and safety of bariatric surgery for craniopharyngioma-related hypothalamic obesity – A matched case-control study with two years of follow-up

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## ABSTRACT

**Background:** Hypothalamic obesity is a devastating consequence of craniopharyngioma. Bariatric surgery could be a promising therapeutic option. However, its efficacy and safety in patients with craniopharyngioma-related hypothalamic obesity remain largely unknown.

**Objectives:** We investigated the efficacy of bariatric surgery for inducing weight loss in patients with craniopharyngioma-related hypothalamic obesity. Additionally, we studied the safety of bariatric surgery regarding its effects on hormone replacement therapy for pituitary insufficiency.

**Methods:** In this retrospective matched case-control study, we compared weight loss after bariatric surgery (i.e. Roux-en-Y gastric bypass and sleeve gastrectomy) between eight patients with craniopharyngioma-related hypothalamic obesity and 75 controls with "common" obesity during two years of follow-up. We validated our results at one year of follow-up in a meta-analysis. Additionally, we studied alterations in hormone replacement therapy after bariatric surgery in patients with craniopharyngioma.

**Results:** Mean weight loss after bariatric surgery was 19% vs. 25% (difference -6%, 95% CI -14.1 to 4.6; *P*=0.091) at two years of follow-up in patients with craniopharyngioma-related hypothalamic obesity compared to control subjects with "common" obesity. Mean weight loss was 25% vs. 29% (difference -4%, 95% CI -11.6 to 8.1; *P*=0.419) after Roux-en-Y gastric bypass, and 10% vs. 20% (difference -10%, 95% CI -14.1 to -6.2; *P*=0.003) after sleeve gastrectomy at two years of follow-up in patients with craniopharyngioma-related hypothalamic obesity vs. control subjects with "common" obesity. Our meta-analysis demonstrated significant weight loss one year after Roux-en-Y gastric bypass, but not after sleeve gastrectomy. Seven patients with craniopharyngioma suffered from pituitary insufficiency; three of them required minor adjustments in hormone replacement therapy after bariatric surgery.

**Conclusions:** Weight loss after Roux-en-Y gastric bypass, but not sleeve gastrectomy, was comparable between patients with craniopharyngioma-related hypothalamic obesity and control subjects with "common" obesity at two years of follow-up. Bariatric surgery seems safe regarding its effects on hormone replacement therapy.

### INTRODUCTION

Craniopharyngiomas are benign epithelial neoplasms located in the sellar and/or suprasellar region of the skull that occur in both children and adults. Their treatment generally consists of neurosurgical excision with or without postoperative radiotherapy.[1] Long-term tumour- and/or treatment-related morbidities, including pituitary hormone deficiencies and morbid obesity related to hypothalamic dysfunction, occur frequently and may result in premature mortality.[2] Hypothalamic obesity and its comorbidities are among the most devastating consequences of craniopharyngioma,[3] and affect approximately 55% of the patients.[4]

Hypothalamic obesity is considered to be an "endogenous" type of obesity, in which hypothalamic damage is postulated to result in autonomic nervous system dysfunction, as well as acquired leptin and insulin resistance, which altogether adversely affect food intake and food satisfaction, metabolism, as well as energy expenditure.[5] Therefore, it seems to be a distinct entity separated from "exogenous" or "common" obesity, in which excessive caloric intake promotes weight gain.[6] Hypothalamic dysfunction is a major contributor to the morbid obesity commonly observed in patients with craniopharyngioma. However, other factors like familial predisposition for obesity and reduced physical activity, which may be related to neurological and visual dysfunction, increased daytime sleepiness, and psychological difficulties may also contribute to excessive weight gain.[7-9] Patients with craniopharyngioma-related hypothalamic obesity experience continuous weight gain that evolves predominantly during the first year after craniopharyngioma treatment.[10, 11] Hypothalamic obesity is, similar to "common" obesity,[6] largely resistant to lifestyle modification.[12] In addition, pharmacological treatment strategies show only modest results coupled with significant side effects.[5] Since bariatric surgery has proven to be highly effective in the "common" obese population,[13] it has been proposed as a therapeutic option for hypothalamic obesity as well.[14] However, studies on the efficacy and safety of bariatric surgery for craniopharyngioma-related hypothalamic obesity remain scarce, and do not compare achieved weight loss with matched control subjects.

Since many patients with craniopharyngioma require hormone replacement therapy for pituitary hormone deficiencies,[2] and bariatric surgery might affect drug absorption and bioavailability,[15] it is important to consider the effects of bariatric procedures on endocrine substitution regimens. This is enforced by differences in pharmacokinetics and pharmacodynamics between obese and lean subjects,[16] which may reasonably change after significant weight loss. Nonetheless, the effects of bariatric surgery on hormone replacement therapy have not been addressed extensively in prior studies. Up until now, only one small study specifically investigated the absorption of hormone replacement therapy in patients with craniopharyngioma after bariatric surgery.[17]

The primary aim of our study was to investigate the efficacy of bariatric surgery for inducing weight loss in patients with craniopharyngioma-related hypothalamic obesity. As secondary aims, we studied the effects of bariatric surgery on hormone replacement therapy and presence of treatment for diabetes mellitus, hypertension, and dyslipidaemia. Accordingly, we performed the first matched case-control study that compared bariatric surgery-induced weight loss between patients with craniopharyngioma-related hypothalamic obesity and control subjects with "common" obesity. We validated our results on bariatric surgery-induced weight loss in patients with craniopharyngioma-related hypothalamic obesity in a meta-analysis. In addition, we investigated the safety of bariatric surgery regarding its effects on hormone replacement therapy for pituitary insufficiency. As a result, we conducted the first study addressing both the efficacy and safety of bariatric surgery in patients with craniopharyngioma-related hypothalamic obesity.

## MATERIALS AND METHODS

### Study participants

In this retrospective matched case-control study, we compared bariatric surgery-induced weight loss between patients with craniopharyngioma-related hypothalamic obesity and control subjects with "common" obesity. Patients with craniopharyngioma who underwent bariatric surgery were identified by a computer-based search in the electronic patient files of the Erasmus University Medical Centre (Rotterdam, the Netherlands), and the Sahlgrenska University Hospital (Gothenburg, Sweden). Eight of such patients were identified (four Dutch and four Swedish patients). In the Dutch cases, all bariatric procedures had been performed at dedicated regional centres experienced in weight-loss surgery. In the Swedish patients, all but one bariatric procedure had been performed at the Sahlgrenska University Hospital. In all eight patients, diagnoses of craniopharyngioma were pathology-proven and craniopharyngioma-related hypothalamic and/or third ventricle damage was demonstrated by neuroimaging. Pituitary hormone deficiencies were diagnosed on the basis of pituitary function testing or complete neurosurgical removal of the pituitary stalk and/or gland.

Patients with craniopharyngioma were individually matched to 6-10 control subjects with "common" obesity, which yielded a total of 75 control participants. Control subjects were derived from the Scandinavian Obesity Surgery Registry (SOReg), which is a Swedish nationwide registry that includes more than 40 000 individuals treated with bariatric surgery from all over the country.[18] Matching was based on the type and date of bariatric procedure, age, gender, preoperative body mass index, and preoperative morbidity (i.e. presence of diabetes mellitus and/or hypertension). Ethical approval was obtained from the local institutional review board of the Erasmus University Medical Centre and the

regional ethical review board in Gothenburg, Sweden. All patients gave their informed consent.

## Outcomes of interest

We compared weight loss between patients with craniopharyngioma-related hypothalamic obesity and control subjects with "common" obesity at six weeks, one year, and two years of follow-up after bariatric procedure. We validated our results on weight loss at one year of follow-up in patients with craniopharyngioma-related hypothalamic obesity in a meta-analysis. In addition, we studied bariatric surgery-induced alterations in hormone replacement therapy for pituitary insufficiency in patients with craniopharyngioma. Furthermore, we compared presence of treatment for diabetes mellitus, hypertension, and dyslipidaemia between patients with craniopharyngioma and control subjects before, as well as one year after bariatric procedure.

Adjustments in the daily recombinant human growth hormone dose, necessary to maintain serum insulin-like growth factor I (IGF-I) levels within the age- and sex-adjusted reference range, represented the influence of bariatric surgery on growth hormone replacement therapy. Adjustments in the daily levothyroxine dose, necessary to maintain serum free thyroxine (fT4) levels within the reference range, were used to express bariatric surgery-induced alterations in thyroid hormone substitution. Hospital admissions for adrenal crises post- vs. pre-bariatric surgery, as well as adjustments in the daily hydrocortisone dose, were used as indicators for bariatric surgery-induced alterations in hydrocortisone therapy. Switches in the oestrogen-progestin replacement therapy preparation due to signs and symptoms of oestrogen deficiency represented the influence of bariatric surgery on oestrogen-progestin replacement therapy. The influence of bariatric surgery on testosterone replacement therapy was assessed by adjustments in the testosterone dose, necessary to keep serum testosterone levels within the reference range. Adjustments in the daily desmopressin dose, required to reach an acceptable amount of fluid intake and diuresis throughout the day, were used as an indicator for bariatric surgery-induced alterations in desmopressin treatment. In addition, changes in hormone replacement therapy formulation type due to signs and symptoms of ineffective endocrine substitution were studied.

## Data collection

Relevant clinical data on patient characteristics, medical status, craniopharyngioma treatment, bariatric surgery, anthropometry, use of hormone replacement therapy, antidiabetic agents, antihypertensive medication, and antihyperlipidemic drugs were retrieved from the medical records of the patients with craniopharyngioma. The Scandinavian Obesity Surgery Registry provided the relevant information regarding the control subjects.

## Statistics

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 24, Chicago, IL, USA) and Review Manager (RevMan version 5.3, The Cochrane Collaboration, 2014). Continuous data were represented as mean ± standard deviation (SD), or median and range. Categorical data were represented as observed frequencies and percentages. Baseline characteristics were compared between patients with craniopharyngioma-related hypothalamic obesity and control subjects with "common" obesity by Mann-Whitney *U*-tests and Fisher's exact tests for numerical and categorical data, respectively. Because of the matched case-control design of our study, weight loss was compared between cases and controls using a one-factor generalized randomized block design. Two-way analyses of variances were performed, in which the matched case-control units were included as blocks. Percentage weight loss at six weeks, one year, and two years were considered dependent variables, and either being a patient with craniopharyngioma or a control subject as the independent variable. Bootstrapping with 1000 replicates was performed since assumptions of two-way analysis of variance were not met initially. Presence of treatment for diabetes mellitus, hypertension, and dyslipidaemia at one year after bariatric procedure was compared between cases and controls using conditional logistic regression. In order to validate our results on bariatric surgery-induced weight loss in patients with craniopharyngioma-related hypothalamic obesity, we performed a meta-analysis in which we compared body mass index at one year of follow-up after bariatric surgery with body mass index at bariatric procedure. We included all patients who received a Roux-en-Y gastric bypass or sleeve gastrectomy for craniopharyngioma-related hypothalamic obesity with sufficient follow-up data at one year after bariatric surgery published previously,[19] and added our own eight patients. This yielded a total of 20 patients. Data were pooled using the inverse variance method with a random-effects model, and mean differences and corresponding 95% confidence intervals (CI) were calculated. We estimated statistical heterogeneity between studies using the $I^2$ statistic.[20] We considered a *P*-value < 0.05 statistically significant.

## RESULTS

### Patient characteristics

Characteristics of the patients with craniopharyngioma are shown in Table 7.1. Six patients were treated for craniopharyngioma at an age < 18 years and two at an age ≥ 18 years. Subsequently, all patients developed hypothalamic obesity for which bariatric surgery was applied a median 13 years (range 2-26 years) after craniopharyngioma treatment. Five patients received a Roux-en-Y gastric bypass, and three a sleeve gastrectomy. One patient underwent a second bariatric procedure (i.e. Roux-en-Y gastric bypass) ap-

**Table 7.1.**

| n | Cohort | Gender | Craniopharyngioma treatment | | | | | | PD | Bariatric surgery | | |
|---|--------|--------|-----------------------------|---|---|---|---|---|-----|-------------------|---|---|
| | | | Age (yr.) | 1st treatment | FU (mo.) | 2nd treatment | FU (mo.) | 3rd treatment | | FU cranio BS (yr.) | Bariatric procedure | BMI (kg/m²) |
| 1 | Dutch | ♀ | 16 | Cyst decompression + Rickham reservoir | - | - | - | - | GH | 26 | SG | 40.9 |
| 2 | Dutch | ♀ | 8 | Complete excision (subfrontal) | - | - | - | - | Panhyp. | 11 | RYGB | 47.1 |
| 3 | Dutch | ♀ | 8 | Complete excision (subfrontal) | 8 | Complete excision (subfrontal) | 7 | Fractionated stereotactic radiotherapy (54 Gy in 30 fractions) | Panhyp. | 13 | RYGB | 49.9 |
| 4 | Dutch | ♀ | 48 | Complete excision (subfrontal) | - | - | - | - | Panhyp. | 2 | RYGB | 42.9 |
| 5 | Swedish | ♀ | 41 | Complete excision (transsphenoidal) | - | - | - | - | GH, TSH | 11 | RYGB | 36.8 |
| 6 | Swedish | ♀ | 10 | Incomplete excision (transcranial) + conventional external beam radiotherapy (45 Gy) | - | - | - | - | Panhyp. | 23 | SG | 44.6 |
| 7 | Swedish | ♂ | 6 | Incomplete excision (subfrontal) + fractionated stereotactic radiotherapy (16 Gy) | - | - | - | - | GH, TSH, HH, DI | 13 | RYGB | 40.5 |
| 8 | Swedish | ♀ | 14 | Complete excision (transsphenoidal) | - | - | - | - | Panhyp. | 14 | SG (+ RYGB after 2 yr.) | 43.7 |

- = no pituitary hormone deficiencies; ♂ = male; ♀ = female; - = not applicable; BMI = body mass index; FU = follow-up; FU cranio BS = follow-up between primary craniopharyngioma treatment and bariatric surgery; DI = diabetes insipidus; GH = growth hormone deficiency; Gy = gray; HH = hypogonadotropic hypogonadism; mo. = months; n = number; Panhyp. = panhypopituitarism; PD = pituitary hormone deficiencies; RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; TSH = secondary hypothyroidism; yr. = years.

proximately two years after a sleeve gastrectomy due to insufficient weight loss. In this patient, only data until the second weight-loss surgery were taken into account.

Baseline characteristics of patients with craniopharyngioma-related hypothalamic obesity compared to matched control subjects with "common" obesity are shown in Table 7.2. Baseline characteristics were comparable, although patients with craniopharyngioma who underwent sleeve gastrectomy were more likely to use antihypertensive medication before bariatric surgery (*P*=0.033).
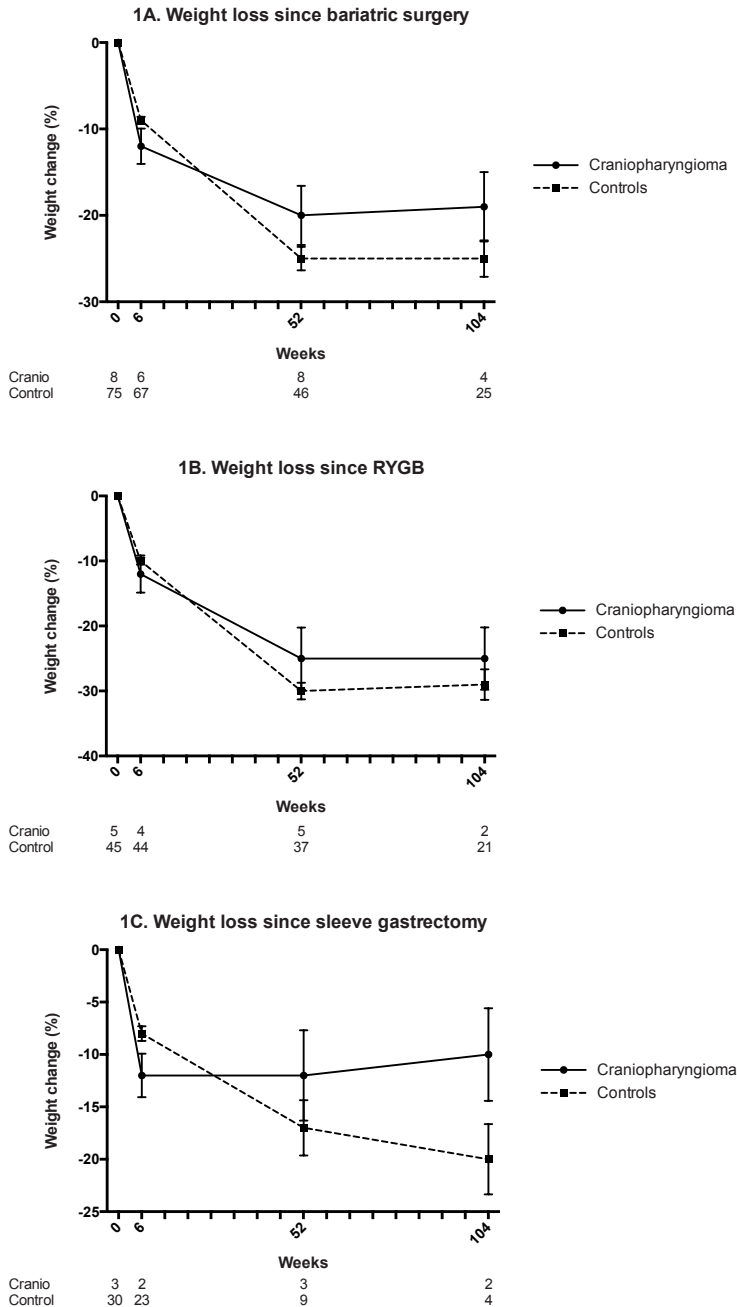
**Table 7.2.**

| Characteristic | Craniopharyngioma | Control |
|---|---|---|
| *n* | 8 | 75 |
| Gender (*n* [%]) | ♂ 1 (12.5) | ♂ 9 (12.0) |
| | ♀ 7 (87.5) | ♀ 66 (88.0) |
| Bariatric procedure (*n* [%]) | | |
| -  Roux-en-Y Gastric bypass | 5 (62.5) | 45 (60.0) |
| -  Sleeve gastrectomy | 3 (37.5) | 30 (40.0) |
| Mean age at bariatric procedure ± SD (yr.) | 33.4 ± 13.6 | 34.2 ± 12.9 |
| -  Roux-en-Y Gastric bypass | 32.6 ± 17.3 | 33.8 ± 16.0 |
| -  Sleeve gastrectomy | 34.7 ± 7.0 | 34.8 ± 6.0 |
| Mean preoperative BMI ± SD (kg/m$^2$) | 43.3 ± 4.1 | 40.3 ± 4.4 |
| -  Roux-en-Y Gastric bypass | 43.4 ± 5.2 | 40.1 ± 3.6 |
| -  Sleeve gastrectomy | 43.1 ± 1.9 | 40.4 ± 4.9 |
| Preoperative DM (*n* [%]) | 1 (12.5) | 6 (8.0) |
| Preoperative HT (*n* [%]) | 4 (50.0) | 13 (17.3) |
| Preoperative dyslipidaemia (*n* [%]) | 1 (12.5) | 2 (2.7) |

♂ = male; ♀ = female; % = percentage; BMI = body mass index; DM = treatment for diabetes mellitus; dyslipidaemia = treatment for dyslipidaemia; HT = treatment for hypertension; kg/m$^2$ = kilograms per square meter; *n* = number; RYGB = Roux-en-Y gastric bypass; SD = standard deviation; SG = sleeve gastrectomy; yr. = years.

**Weight loss after bariatric surgery**

Weight loss after bariatric surgery in patients with craniopharyngioma-related hypothalamic obesity compared to control subjects with "common" obesity is shown in Figure 7.1. Mean percentage weight loss after bariatric surgery was 12% vs. 9% (difference 3%, 95% CI -2.0 to 6.2; *P*=0.196) at six weeks, 20% vs. 25% (difference -5%, 95% CI -11.7 to 2.2; *P*=0.141) at one year, and 19% vs. 25% (difference -6%, 95% CI -14.1 to 4.6; *P*=0.091) at two years of follow-up in patients with craniopharyngioma-related hypothalamic obesity compared to control subjects with "common" obesity. After Roux-en-Y gastric bypass, mean percentage weight loss was 12% vs. 10% (difference 2%, 95% CI -4.2 to 8.1; *P*=0.443) at six weeks, 25% vs. 30% (difference -5%, 95% CI -14.4 to 5.2; *P*=0.257)

**Figure 7.1.** Mean percentage weight loss (± bootstrapped standard error) after bariatric surgery in patients with craniopharyngioma-related hypothalamic obesity compared to control subjects with "common" obesity.



**1A. Weight loss since bariatric surgery**

| | | | | | |
|---|---|---|---|---|---|
| Cranio | 8 | 6 | | 8 | 4 |
| Control | 75 | 67 | | 46 | 25 |



**1B. Weight loss since RYGB**

| | | | | | |
|---|---|---|---|---|---|
| Cranio | 5 | 4 | | 5 | 2 |
| Control | 45 | 44 | | 37 | 21 |



**1C. Weight loss since sleeve gastrectomy**

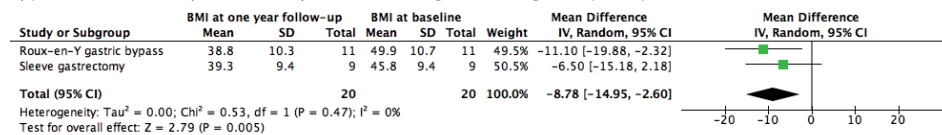| | | | | | |
|---|---|---|---|---|---|
| Cranio | 3 | 2 | | 3 | 2 |
| Control | 30 | 23 | | 9 | 4 |

(A) Both bariatric procedures combined. (B) Roux-en-Y gastric bypass. (C) Sleeve gastrectomy. % = percentage; Cranio = patients with craniopharyngioma; RYGB = Roux-en-Y gastric bypass.

at one year, and 25% vs. 29% (difference -4%, 95% CI -11.6 to 8.1; *P*=0.419) at two years of follow-up in patients with craniopharyngioma-related hypothalamic obesity vs. control subjects with "common" obesity. Mean percentage weight loss after sleeve gastrectomy was 12% vs. 8% (difference 4%, 95% CI -1.3 to 6.9; *P*=0.117) at six weeks, 12% vs. 17% (difference - 5%, 95% CI -15.5 to 3.2; *P*=0.334) at one year, and 10% vs. 20% (difference -10%, 95% CI -14.1 to -6.2; *P*=0.003) at two years of follow-up in patients with craniopharyngioma-related hypothalamic obesity vs. control subjects with "common" obesity. All but one patient with craniopharyngioma lost weight markedly after bariatric surgery. We have no clear explanation for the weight-loss failure in this particular patient who underwent a sleeve gastrectomy.

We validated our results on bariatric-surgery induced weight loss in patients with craniopharyngioma-related hypothalamic obesity by performing a meta-analysis in which we compared body mass index at one year of follow-up after bariatric surgery with body mass index at bariatric procedure (Figure 7.2). We observed significant weight loss after bariatric surgery (mean 8.78, 95% CI 2.60 to 14.95 kg/m$^2$). Although Roux-en-Y gastric bypass resulted in significant weight loss (mean 11.10, 95% CI 2.32 to 19.88 kg/m$^2$), sleeve gastrectomy was less effective (mean 6.50, 95% CI -2.18 to 15.18 kg/m$^2$).

**Figure 7.2.** Forest plot on the mean difference in body mass index at one year of follow-up after bariatric surgery compared to body mass index at bariatric procedure in patients with craniopharyngioma-related hypothalamic obesity. BMI = body mass index; kg/m$^2$ = kilograms per square meter.



| Study or Subgroup | BMI at one year follow-up | | | BMI at baseline | | | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Total | Mean | SD | Total | | | |
| Roux–en–Y gastric bypass | 38.8 | 10.3 | 11 | 49.9 | 10.7 | 11 | 49.5% | -11.10 [-19.88, -2.32] | |
| Sleeve gastrectomy | 39.3 | 9.4 | 9 | 45.8 | 9.4 | 9 | 50.5% | -6.50 [-15.18, 2.18] | |
| | | | | | | | | | |
| Total (95% CI) | | | 20 | | | 20 | 100.0% | -8.78 [-14.95, -2.60] | |
| Heterogeneity: Tau$^2$ = 0.00; Chi$^2$ = 0.53, df = 1 (P = 0.47); I$^2$ = 0% | | | | | | | | | |
| Test for overall effect: Z = 2.79 (P = 0.005) | | | | | | | | | |

### Effects of bariatric surgery on hormone replacement therapy

Effects of bariatric surgery on hormone replacement therapy are shown in Table 7.3. Seven of eight patients with craniopharyngioma used hormone replacement therapy for pituitary insufficiency. In the patients using growth hormone replacement, serum IGF-I levels declined during the first year after bariatric surgery in all but one patient (data not shown). In two patients, this enforced a minor increase in the daily recombinant human growth hormone dose. The daily levothyroxine dose was reduced in three patients during the first twelve months after bariatric surgery. No patients were admitted to the hospital for adrenal crisis pre- or post-bariatric procedure. In addition, no adjustments in the daily hydrocortisone dose were necessary. One patient switched from oestradiol 2 mg/dydrogesteron 10 mg oestrogen-progestin replacement to ethinyloestradiol 30 µg/levonorgestrel 150 µg approximately two months after bariatric procedure; five months later she switched to ethinyloestradiol 50 µg/levonorgestrel 125 µg. No adjustments in

**Table 7.3.**

| n | Cohort | Growth hormone (mg/day) | | | | Levothyroxine (mg/day) | | | | Hydrocortisone (mg/day) | | | | Sex steroids | | Desmopressin (mg/day) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | BS | 6 wk. | 1 yr. | 2 yr. | BS | 6 wk. | 1 yr. | 2 yr. | BS | 6 wk. | 1 yr. | 2 yr. | Preparation BS | Preparation during ≥ 1 yr. | BS | 6 wk. | 1 yr. | 2 yr. |
| 1 | Dutch | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| 2 | Dutch | 0.50 | 0.50 | 0.60 | 0.60 | 200 | 200 | 175 | 175 | 20 | 20 | 20 | 20 | Oestradiol 2mg Dydrogesteron 10mg | Oestradiol 2mg Dydrogesteron 10mg | 0.30 | 0.30 | 0.40 | 0.40 |
| 3 | Dutch | 2.40 | 2.40 | 2.80 | NA | 200 | 175 | 175 | NA | 20 | 20 | 20 | NA | Oestradiol 2mg Dydrogesteron 10mg | Ethinyloestradiol 50µg Levonorgestrel 125µg | 0.15 | 0.15 | 0.15 | NA |
| 4 | Dutch | 0.30 | 0.30 | 0.30 | 0.25 | 150 | 150 | 150 | 150 | 20 | 20 | 20 | 20 | - | - | 0.30 | 0.35 | 0.35 | 0.35 |
| 5 | Sweden | 0.15 | 0.15 | 0.15 | 0.15 | 175 | 175 | 175 | 175 | - | - | - | - | - | - | - | - | - | - |
| 6 | Sweden | 0.80 | 0.80 | 0.80 | NA | 350 | 350 | 250 | NA | 20 | 20 | 20 | NA | Oestradiol 2mg Norethisterone 1mg | Oestradiol 2mg Norethisterone 1mg | 0.05 | 0.05 | 0.05 | NA |
| 7 | Sweden | 1.40 | 1.40 | 1.40 | NA | 200 | 200 | 200 | NA | - | - | - | NA | Testosterone 1000mg i.m. every 3 mo. | Testosterone 1000mg i.m. every 3 mo. | 0.10 | 0.10 | 0.10 | NA |
| 8 | Sweden | 0.60 | 0.60 | - | - | 175 | 175 | 175 | 175 | 20 | 20 | 20 | 20 | Oestradiol 2mg Norethisterone 1mg | Oestradiol 2mg Norethisterone 1mg | 0.06 | 0.06 | 0.06 | 0.06 |

Recombinant human growth hormone was administered as a daily subcutaneous injection; levothyroxine, hydrocortisone, oestrogen-progestin replacement therapy, and desmopressin were administered as daily oral tablets. Testosterone was administered as an intramuscular injection. - = no use of endocrine substitution therapy; µg = microgram; BS = bariatric surgery; mg = milligram; n = number; NA = not available; Preparation during ≥ 1 yr. FU = preparation after at least one year of follow-up after bariatric surgery; Preparation BS = preparation at bariatric surgery; wk. = weeks, yr. = years.

the prescribed testosterone replacement therapy were required after bariatric surgery. In two of six patients using desmopressin, the daily dose had to be slightly increased after bariatric surgery. No patient required any change in formulation type of endocrine substitution therapy.

### Diabetes mellitus, hypertension, and dyslipidaemia

Presence of treatment for diabetes mellitus, hypertension, and dyslipidaemia before, as well as one year after bariatric surgery in patients with craniopharyngioma-related hypothalamic obesity compared to control subjects with "common" obesity is shown in Table 7.4. At one year of follow-up after bariatric surgery, there were no significant differences in the use of antidiabetic, antihypertensive, and antihyperlipidemic agents between cases and controls. Presence of treatment for diabetes mellitus, hypertension, and dyslipidaemia in patients with craniopharyngioma before and one year after bariatric surgery was 12.5% vs. 0%, 50.0% vs. 25.0%, and 12.5% vs. 12.5%, respectively.

**Table 7.4.**

| | Both procedures | | | RYGB | | | SG | | |
|---|---|---|---|---|---|---|---|---|---|
| | Craniopharyngioma | Control | P-value | Craniopharyngioma | Control | P-value | Craniopharyngioma | Control | P-value |
| **Diabetes mellitus: *n* (%)** | | | | | | | | | |
| - Before BS | 1 (12.5) | 6 (8.0) | NS | 1 (20.0) | 6 (13.3) | NS | 0 | 0 | NS |
| - 1 yr. FU | 0 | 2 (2.7) | NS | 0 | 2 (4.4) | NS | 0 | 0 | NS |
| **Hypertension: *n* (%)** | | | | | | | | | |
| - Before BS | 4 (50.0) | 13 (17.3) | NS | 2 (40.0) | 11 (24.4) | NS | 2 (66.7) | 2 (6.7) | 0.021 |
| - 1 yr. FU | 2 (25.0) | 17 (22.7) | NS | 1 (20.0) | 14 (31.1) | NS | 1 (33.3) | 3 (10.0) | NS |
| **Dyslipidaemia: *n* (%)** | | | | | | | | | |
| - Before BS | 1 (12.5) | 2 (2.7) | NS | 0 | 1 (2.2) | NS | 1 (33.3) | 1 (3.3) | NS |
| - 1 yr. FU | 1 (12.5) | 0 | NS | 0 | 0 | NS | 1 (33.3) | 0 | NS |

% = percentage; BS = bariatric surgery; FU = follow-up; *n* = number; NS = not significant; RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; yr. = years.

## DISCUSSION

This matched case-control study is the first to address two of the most important clinical questions on bariatric surgery for craniopharyngioma-related hypothalamic obesity: does bariatric surgery results in sufficient weight loss, and is bariatric surgery

safe regarding its effects on hormone replacement therapy for pituitary insufficiency? We compared bariatric surgery-induced weight loss between patients with craniopharyngioma-related hypothalamic obesity and extensively matched control subjects with "common" obesity. Additionally, we validated our results on weight loss in patients with craniopharyngioma-related hypothalamic obesity in a meta-analysis. Moreover, we investigated the effects of bariatric surgery on hormone replacement therapy for pituitary insufficiency. At two years of follow-up, weight loss after Roux-en-Y gastric bypass, but not sleeve gastrectomy, was comparable between patients with craniopharyngioma-related hypothalamic obesity and control subjects with "common" obesity. Accordingly, our meta-analysis revealed significant weight loss after Roux-en-Y gastric bypass at one year of follow-up after bariatric surgery in patients with craniopharyngioma-related hypothalamic obesity; sleeve gastrectomy was less effective. Minor adjustments in hormone replacement therapy were required in three of seven patients with craniopharyngioma.

One other case-control study compared weight loss after bariatric surgery between patients with craniopharyngioma-related hypothalamic obesity and control subjects with "common" obesity. In this retrospective non-matched study, Weismann et al. included nine patients with craniopharyngioma and 143 control subjects. In their study, two patients with craniopharyngioma received a Roux-en-Y gastric bypass, and four a sleeve gastrectomy.[21] In concordance with our results, weight loss after bariatric surgery was only comparable between cases and controls in the subset of patients who received a Roux-en-Y gastric bypass. In the study by Weismann et al., control subjects were significantly older and presented more pronounced metabolic disturbances at baseline compared to patients with craniopharyngioma.[21] In the present study, we validated our results on bariatric surgery-induced weight loss in patients with craniopharyngioma-related hypothalamic obesity by performing a meta-analysis. Consequently, we updated a previous meta-analysis by Bretault et al.[19] This prior meta-analysis studied weight loss at six months and one year of follow-up after bariatric surgery and could not demonstrate significant weight loss after Roux-en-Y gastric bypass or sleeve gastrectomy.

At the moment, it is still largely unknown by what exact mechanisms bariatric procedures establish their effects. Alterations in eating behaviour and energy homeostasis due to a combination of changes in gut hormone and autonomous nervous system signalling are thought to be responsible for weight loss and improved glycaemic control. Bariatric surgery-induced alterations in blood bile acid concentrations and gut microbiota may also contribute to weight decline.[22] Hypothalamic structures, like the ventromedial nucleus, arcuate nucleus, paraventricular nucleus, lateral hypothalamic area, dorsomedial nucleus, dorsal hypothalamic area, supraoptic nucleus, and suprachiasmatic nucleus are key regulators in balancing feeding behaviour and energy expenditure by integrating gut hormone and autonomous nervous system signalling.[5, 23] Craniopharyngiomas and/

or their treatment may damage these important brain structures, thereby resulting in autonomic nervous system dysfunction and acquired leptin and insulin resistance, which subsequently adversely alter food intake and food satisfaction, metabolism, as well as energy expenditure.[5] This could diminish the efficacy of bariatric procedures like Roux-en-Y gastric bypass and sleeve gastrectomy, which may rely, at least partly, on intact hypothalamic function for their beneficial effects.[24] However, we observed a weight loss similar to control subjects with "common" obesity in most of our patients with craniopharyngioma-related hypothalamic obesity after bariatric surgery. This may be explained by the observation that brain circuits and gut hormone receptors thought to be important in exerting beneficial effects of bariatric procedures are not only found in the hypothalamus, but in other brain regions probably not affected by the craniopharyngioma and/or its treatment as well.[24] Consequently, weight-loss-promoting changes in gut hormone and autonomous nervous system signalling can probably still exert some of their beneficial effects in patients with craniopharyngioma-related hypothalamic obesity.

Bariatric procedures potentially influence drug absorption and bioavailability.[15] In addition, pharmacokinetics and pharmacodynamics, which are different in obese and lean subjects,[16] may reasonably change following weight loss, possibly resulting in altered drug dose requirements. Therefore, it is important to consider the effects of bariatric surgery on hormone replacement therapy for pituitary insufficiency in patients with craniopharyngioma. In our study, seven patients with craniopharyngioma used endocrine substitution regimens. Bariatric surgery did not seem to affect hormone replacement therapy significantly, although one might expect lower levothyroxine requirements due to the bariatric surgery-induced weight loss.[25] Therefore, it seems likely that the absorption of some hormones might be decreased. Other studies addressing bariatric surgery-induced alterations in hormone replacement therapy are scarce. A recent study by Wolf et al. reported no significant changes in the administered daily recombinant human growth hormone, levothyroxine, hydrocortisone, and desmopressin dose in four patients with craniopharyngioma at 13-65 months of follow-up after gastric bypass compared to baseline. In addition, no adrenal crises were observed. An oral thyroid/hydrocortisone absorption test, which was performed in one patient after bariatric surgery, revealed adequate drug absorption.[17] Given the bariatric surgery-induced weight loss, the hydrocortisone need is expected to be reduced. Therefore, using the same hydrocortisone dose after compared to before bariatric surgery may induce steroid-related side-effects like weight gain, unless the bioavailability of hydrocortisone is reduced.[26] However, this has not been systematically studied.

At one year of follow-up after bariatric surgery, there were no significant differences in the use of antidiabetic, antihypertensive, and antihyperlipidemic agents between patients with craniopharyngioma-related hypothalamic obesity and control subjects with

"common" obesity. In patients with craniopharyngioma, the presence of treatment for diabetes mellitus and hypertension declined at one year of follow-up after bariatric surgery compared to baseline, while the use of hypolipidemic medication remained equal. In the aforementioned study by Bretault et al., 31.6% of patients with craniopharyngioma-related hypothalamic obesity were diabetic at bariatric procedure. This declined to 8.3% at one year of follow-up. One patient required antihypertensive medication before bariatric surgery. No data on antihyperlipidemic drugs were available.[19]

Our study has some limitations. Since craniopharyngioma is a rare disease, and only a minority of patients with craniopharyngioma is likely to have undergone bariatric surgery, it is hard to obtain a large sample size, even with international collaboration. In an attempt to overcome this issue, we performed a meta-analysis to validate our results on bariatric surgery-induced weight loss in patients with craniopharyngioma-related hypothalamic obesity. However, due to the relatively small number of patients, results of statistical analyses have to be interpreted cautiously. In addition, we were unable to report perioperative and postoperative complications of bariatric surgery in all patients with craniopharyngioma. Only data from the Swedish patients were available on this subject, in whom only one patient suffered from postoperative abdominal pain during the first six weeks after sleeve gastrectomy. In the study by Weismann et al., the occurrence of postoperative problems after bariatric surgery (i.e. abdominal pain, vomiting, and reflux) was similar in patients with craniopharyngioma-related hypothalamic obesity and control subjects with "common" obesity.[21]

In conclusion, our observations suggest that bariatric surgery, in particular with Roux-en-Y gastric bypass, might be an effective therapeutic option for craniopharyngioma-related hypothalamic obesity without significant side-effects on hormone replacement therapy for pituitary insufficiency. However, careful drug monitoring is still advised, especially for levothyroxine and hydrocortisone. Larger, international, well-designed studies are needed to receive more efficacy and safety data regarding the therapeutic potential of bariatric surgery for craniopharyngioma-related hypothalamic obesity. Such studies should have an adequate follow-up duration and should compare weight loss between patients and matched control subjects.

## REFERENCES

1. Muller HL. Craniopharyngioma. *Endocr Rev* 2014 er20131115.
2. 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. *J Clin Endocrinol Metab* 2015 **100** 467-474.
3. Muller HL, Faldum A, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R & Sorensen N. Functional capacity, obesity and hypothalamic involvement: cross-sectional study on 212 patients with childhood craniopharyngioma. *Klin Padiatr* 2003 **215** 310-314.
4. Muller HL, Gebhardt U, Etavard-Gorris N, Korenke E, Warmuth-Metz M, Kolb R, Sorensen N & Calaminus G. Prognosis and sequela in patients with childhood craniopharyngioma -- results of HIT-ENDO and update on KRANIOPHARYNGEOM 2000. *Klin Padiatr* 2004 **216** 343-348.
5. 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** 1774-1797.
6. Haslam DW & James WP. Obesity. *Lancet* 2005 **366** 1197-1209.
7. Muller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, Korinthenberg R, Bettendorf M, Kuhl J, Gutjahr P, Sorensen N & Calaminus G. Obesity after childhood craniopharyngioma--German multicenter study on pre-operative risk factors and quality of life. *Klin Padiatr* 2001 **213** 244-249.
8. Muller HL. Craniopharyngioma and hypothalamic injury: latest insights into consequent eating disorders and obesity. *Curr Opin Endocrinol Diabetes Obes* 2016 **23** 81-89.
9. Roemmler-Zehrer J, Geigenberger V, Stormann S, Ising M, Pfister H, Sievers C, Stalla GK & Schopohl J. Specific behaviour, mood and personality traits may contribute to obesity in patients with craniopharyngioma. *Clin Endocrinol (Oxf)* 2015 **82** 106-114.
10. Muller HL, Emser A, Faldum A, Bruhnken G, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R & Sorensen N. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. *J Clin Endocrinol Metab* 2004 **89** 3298-3305.
11. Roth CL, Eslamy H, Werny D, Elfers C, Shaffer ML, Pihoker C, Ojemann J & Dobyns WB. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. *Obesity (Silver Spring)* 2015 **23** 1226-1233.
12. 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** 1768-1774.
13. Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. *J Intern Med* 2013 **273** 219-234.
14. Inge TH, Pfluger P, Zeller M, Rose SR, Burget L, Sundararajan S, Daniels SR & Tschop MH. Gastric bypass surgery for treatment of hypothalamic obesity after craniopharyngioma therapy. *Nat Clin Pract Endocrinol Metab* 2007 **3** 606-609.
15. Padwal R, Brocks D & Sharma AM. A systematic review of drug absorption following bariatric surgery and its theoretical implications. *Obes Rev* 2010 **11** 41-50.
16. Knibbe CA, Brill MJ, van Rongen A, Diepstraten J, van der Graaf PH & Danhof M. Drug disposition in obesity: toward evidence-based dosing. *Annu Rev Pharmacol Toxicol* 2015 **55** 149-167.
17. Wolf P, Winhofer Y, Smajis S, Kruschitz R, Schindler K, Gessl A, Riedl M, Vila G, Raber W, Langer F, Prager G, Ludvik B, Luger A & Krebs M. Hormone Substitution after Gastric Bypass Surgery in Patients with Hypopituitarism Secondary to Craniopharyngioma. *Endocr Pract* 2016.

18.   Hedenbro JL, Naslund E, Boman L, Lundegardh G, Bylund A, Ekelund M, Laurenius A, Moller P, Olbers T, Sundbom M, Ottosson J & Naslund I. Formation of the Scandinavian Obesity Surgery Registry, SOReg. *Obes Surg* 2015 **25** 1893-1900.

19.   Bretault M, Boillot A, Muzard L, Poitou C, Oppert JM, Barsamian C, Gatta B, Muller H, Weismann D, Rottembourg D, Inge T, Veyrie N, Carette C & Czernichow S. Clinical review: Bariatric surgery following treatment for craniopharyngioma: a systematic review and individual-level data meta-analysis. *J Clin Endocrinol Metab* 2013 **98** 2239-2246.

20.   Higgins JP, Thompson SG, Deeks JJ & Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003 **327** 557-560.

21.   Weismann D, Pelka T, Bender G, Jurowich C, Fassnacht M, Thalheimer A & Allolio B. Bariatric surgery for morbid obesity in craniopharyngioma. *Clin Endocrinol (Oxf)* 2013 **78** 385-390.

22.   Madsbad S, Dirksen C & Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. *Lancet Diabetes Endocrinol* 2014 **2** 152-164.

23.   Coomans CP, van den Berg SA, Lucassen EA, Houben T, Pronk AC, van der Spek RD, Kalsbeek A, Biermasz NR, Willems van Dijk K, Romijn JA & Meijer JH. The suprachiasmatic nucleus controls circadian energy metabolism and hepatic insulin sensitivity. *Diabetes* 2013 **62** 1102-1108.

24.   Rao RS. Bariatric surgery and the central nervous system. *Obes Surg* 2012 **22** 967-978.

25.   Fierabracci P, Martinelli S, Tamberi A, Piaggi P, Basolo A, Pelosini C, Ricco I, Magno S, Querci G, Ceccarini G, Scartabelli G, Salvetti G, Vitti P & Santini F. Weight Loss and Variation of Levothyroxine Requirements in Hypothyroid Obese Patients After Bariatric Surgery. *Thyroid* 2016 **26** 499-503.

26.   Mah PM, Jenkins RC, Rostami-Hodjegan A, Newell-Price J, Doane A, Ibbotson V, Tucker GT & Ross RJ. Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. *Clin Endocrinol (Oxf)* 2004 **61** 367-375.

# Chapter 8

## General discussion and conclusions

## GENERAL DISCUSSION AND CONCLUSIONS

During the past decades, cancer survival increased substantially in both children and adults.[1-4] This resulted in an increased awareness of and insight in long-term consequences of cancer and its treatment.[5-10] Accordingly, a high prevalence of chronic health conditions has been reported in childhood and adult cancer survivors, particularly due to endocrine and metabolic disorders.[11-18] Research on long-term consequences of cancer and its treatment focused predominantly on individuals with a malignant tumour. This is illustrated by the recently started studies from the Late Effects of Childhood Cancer task force of the Dutch Childhood Oncology Group (DCOG-LATER).[19] However, some benign neoplasms, including craniopharyngiomas, may also cause substantial long-term health effects.

The aim of this thesis was to examine long-term endocrine and metabolic conditions, as well as their determinants in patients treated for cancer with a special focus on patients treated for craniopharyngioma. We found that not only patients treated for a malignant tumour, but also patients treated for a benign neoplasm (i.e. craniopharyngioma), experience a high frequency of long-term endocrine and metabolic disorders. In patients with craniopharyngioma, such disorders are mainly due to tumour- and treatment-related damage of critical neurovascular structures (e.g. hypothalamus, pituitary, optic nerves, carotid arteries), as well as their associated morbidities (e.g. obesity related to hypopituitarism). We identified the metabolic syndrome (MetS) and its components as important long-term health conditions in patients with craniopharyngioma, likely to be largely responsible for the excessive morbidity and mortality due to type 2 diabetes mellitus (T2DM) and circulatory diseases in this patient population. At last, we demonstrated that bariatric surgery may be an effective and safe therapy for obesity in patients with craniopharyngioma. The main findings of this thesis are summarized in Figure 8.1.

> **KEY POINT:**
> The aim of this thesis was to examine long-term endocrine and metabolic conditions, as well as their determinants in patients treated for cancer with a special focus on patients treated for craniopharyngioma.

### Long-term endocrine and metabolic consequences of cancer and its treatment

The development of a subsequent neoplasm is an important long-term health condition after cancer treatment.[20] Endocrine-related cancers are among the most common secondary tumours in both childhood and adult cancer survivors.[4, 21] In **Chapter 2**, we reviewed the literature on risk factors for subsequent endocrine-related cancer in childhood cancer survivors. Thereby, we focused on secondary neoplasms of the breast and thyroid.

**Figure 8.1.** Main findings of this thesis
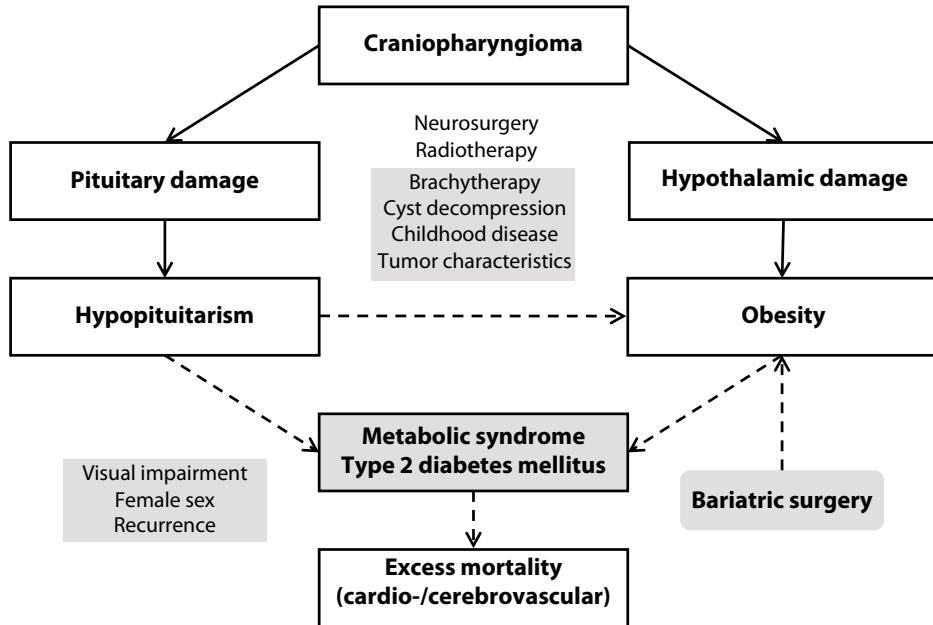


Dashed arrows and grey boxes indicate new findings.

We identified the potential harmful effects of oestrogen-progestin replacement therapy on radiation-induced breast cancer development in premature ovarian insufficient childhood cancer survivors as the most important area for future research. Several studies reported a protective effect of premature ovarian insufficiency on radiation-induced breast cancer development.[22-26] Accordingly, concerns have raised regarding the safety of oestrogen-progestin replacement therapy. However, although available evidence is weak, no clear detrimental effect of oestrogen-progestin replacement therapy on the risk for radiation-induced breast cancer development in premature ovarian insufficient childhood cancer survivors has been demonstrated.[27] Since untreated premature ovarian insufficiency is associated with significant side effects,[28] the use of oestrogen-progestin replacement therapy should not be discouraged in premature ovarian insufficient childhood cancer survivors treated with chest irradiation until clear harmful effects have been demonstrated. Future studies are needed to ascertain the safety of oestrogen-progestin replacement therapy. Meanwhile, oestrogen-progestin replacement therapy could be prescribed based on shared decision-making.

The MetS is another important long-term health condition in cancer survivors.[29-31] It can be defined as a constellation of obesity, insulin resistance, dyslipidaemia, and elevated blood pressure,[32] and has been associated with a two-fold increased risk for cardio- and cerebrovascular disease, as well as a five-fold increased risk for T2DM.[33] An

unhealthy lifestyle with insufficient physical activity seems an important risk factor for the MetS.[34, 35] Accordingly, in **Chapter 3**, we studied daily life physical activity in survivors of nephroblastoma and neuroblastoma. Thereby, we performed one of the first studies that investigated physical activity relative to a non-cancer control group using a validated questionnaire.[36]

We observed a significantly lower level of physical activity in male neuroblastoma survivors compared to male control subjects. Female neuroblastoma survivors and male and female nephroblastoma survivors had similar physical activity levels compared to control subjects. Our results concerning male neuroblastoma survivors confirmed the results of a previous study by Ness et al. that investigated physical activity using a non-validated questionnaire.[37] Other studies in childhood cancer survivors reported particularly low levels of physical activity in individuals treated for brain cancer and osteosarcoma.[38, 39] Most studies in adult cancer survivors focused on individuals treated for breast and colorectal cancer.[39] Consistent with a low level of physical activity, survivors of these malignancies demonstrate a high prevalence of the MetS.[29, 30, 40, 41]

Our results indicate that physical inactivity contributes to the development of the MetS in childhood cancer survivors. Therefore, we advocate a healthy lifestyle with sufficient exercise; all the more because sufficient physical activity has been shown to ameliorate the MetS in childhood and adult cancer survivors.[42] Future studies should use objective methods to measure physical activity.[43] In addition, lifestyle interventions that aim to increase exercise should be developed and evaluated.

**KEY POINTS:**

The potential harmful effects of oestrogen-progestin replacement therapy on radiation-induced breast cancer development in premature ovarian insufficient childhood cancer survivors is an important area for future research.

An unhealthy lifestyle with insufficient physical activity seems to contribute to the development of the MetS in childhood cancer survivors. Lifestyle interventions that aim to increase exercise should be developed and evaluated.

**Long-term endocrine and metabolic consequences in patients with craniopharyngioma**

Not only malignant tumours, but also benign neoplasms, may result in significant long-term tumour- and treatment-related morbidities. An important example of such a benign neoplasm is craniopharyngioma. In **Chapter 4**, we investigated long-term health conditions in a large single-centre cohort of patients treated for craniopharyngioma. We observed pituitary hormone deficiencies, visual impairment, and obesity to be the most

common long-term health effects in 98%, 75%, and 56% of the patients, respectively. Our results confirm previous studies on long-term sequelae of craniopharyngioma treatment.[44-49] In patients with craniopharyngioma, long-term health conditions are mainly due to tumour- and treatment-related damage of critical neurovascular structures and their associated morbidities.[50]

Modern craniopharyngioma treatment aims to minimize long-term tumour- and treatment-related sequelae while providing adequate survival and disease control.[51] Although there is consensus about the fact that hypothalamic and optic functions should be preserved, it remains unknown whether the optimal treatment strategy should be aggressive or more conservative. Accordingly, in **Chapter 4**, we examined long-term sequelae of craniopharyngioma treatment according to the initial therapeutic approach. Thereby, we performed one of the first studies that evaluated long-term health effects of craniopharyngioma treatment with [90]Yttrium brachytherapy and cyst drainage.

After a median follow-up period of 13 years, we observed a similar spectrum of long-term health conditions in patients treated with gross total resection, subtotal resection with or without radiotherapy, [90]Yttrium brachytherapy, and cyst drainage. Recurrence-free survival was significantly lower after cyst drainage compared to the other treatment strategies. Our results confirm previous studies,[45, 52, 53] and indicate that long-term tumour- and treatment-related health effects are frequent in patients with craniopharyngioma, irrespective of the initial treatment strategy.

When interpreting our results, it is important to recognize that the treatment of craniopharyngiomas is predominantly individualized based on tumour and patient characteristics. Therefore, selection bias may have, at least in part, affected our findings. Ideally, a multi-institutional prospective randomized trial should be performed to determine the optimal initial craniopharyngioma treatment strategy. Such a trial should not only study endocrine and metabolic endpoints, but also other conditions like neurological deficits, neurocognitive and neurobehavioral dysfunction, and quality of life.

In **Chapter 4**, we also performed one of the first studies that examined long-term health conditions in patients with craniopharyngioma according to the age at diagnosis. We observed a significantly higher frequency of pituitary hormone deficiencies, morbid obesity, epilepsy, and psychiatric conditions in patients with childhood- compared to adult-onset craniopharyngioma. In addition, we demonstrated that these findings are, at least partly, likely to be due to differences in tumour characteristics already present at diagnosis. Our results are in concordance with a previous study by Gautier et al.[46]

We observed significantly more multicystic tumours, as well as tumours associated with hydrocephalus and hypothalamic damage in patients with childhood- compared to adult-onset craniopharyngioma. Gautier et al. observed significantly more suprasellar tumours with intrasellar extension, as well as a trend towards larger tumours in patients with childhood-onset disease.[46] These results indicate that craniopharyngiomas in chil-

dren are diagnosed when significant progression of the tumour has already occurred. Indeed, Müller et al. reported that most children with craniopharyngioma already present a reduced growth rate 7.5 years before diagnosis.[54] Physicians should be more vigilant of the possibility of a craniopharyngioma in children with growth failure. Future studies should identify other features that may lead to a prompter diagnosis of craniopharyngioma in children, as well as investigate other factors that may explain the significantly higher frequency of long-term health conditions in patients with childhood- compared to adult-onset craniopharyngioma.

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**KEY POINTS:**

In patients with craniopharyngioma, long-term health conditions are mainly due to tumour- and treatment-related damage of critical neurovascular structures and their associated conditions. Pituitary hormone deficiencies, visual impairment, and obesity are the most common long-term health effects.

Long-term tumour- and treatment-related health conditions are frequent in patients with craniopharyngioma, irrespective of their initial treatment strategy.

Long-term health effects are generally more common in patients with childhood- compared to adult-onset craniopharyngioma. This seems, at least partly, to be due to differences in tumour characteristics already present at diagnosis.

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Studies that evaluate long-term health conditions relative to a control population may more reliably identify excess morbidity and mortality than studies that directly examine long-term health effects.[55] Accordingly, in **Chapter 5**, we performed one of the first studies that investigated morbidity and mortality in patients with craniopharyngioma relative to the general population. We studied a large cohort of Dutch and Swedish patients with craniopharyngioma and evaluated many risk factors for excess morbidity and mortality.

We observed patients with craniopharyngioma to have a significantly increased risk for morbidity due to T2DM and cerebral infarction, as well as total mortality and mortality due to circulatory and respiratory diseases. We identified female sex, childhood-onset craniopharyngioma, hydrocephalus, tumour recurrence, and panhypopituitarism as important risk factors for excess morbidity and mortality. Our results confirm previous studies,[56-61] and indicate that patients with craniopharyngioma experience excessive morbidity and mortality relative to the general population.

As indicated above, the increased risk for morbidity and mortality in patients with craniopharyngioma may be explained by tumour- and treatment-related damage of critical neurovascular structures, as well as their associated conditions. Hypothalamic damage

may result in acquired leptin and insulin resistance, as well as in autonomic nervous system dysfunction, which may altogether adversely affect food intake, metabolism, and energy expenditure, thereby promoting obesity and its associated metabolic derangements.[62] Hypopituitarism adversely affects metabolism due to inadequately treated pituitary hormone deficiencies and currently available hormone replacement regimens that do not appropriately simulate hypothalamic-pituitary physiology.[63] This latter explanation may also apply to the excessive morbidity and mortality associated with female sex,[64] and indicates that currently available sex hormone replacement regimens could be improved. New hormone replacement regimens that better mimic the physiological situation should be developed.

Although many potential risk factors for morbidity and mortality in patients with craniopharyngioma are interrelated, hypothalamic damage and hypopituitarism seem to be the principal factors resulting in an adverse health status. Therefore, craniopharyngioma treatment should aim to preserve hypothalamic and pituitary functions and provide optimal endocrine care. To date, most studies in patients with craniopharyngioma used neuroimaging to define hypothalamic involvement without considering clinical features of hypothalamic dysfunction. Although several classification systems for hypothalamic involvement have been developed,[65-68] most of them lack proper validation and are, therefore, not used in clinical practice. Recently, Mortini et al. validated some of these classification systems regarding their correlation with obesity.[69] Future studies should use these validated classification systems and investigate their correlation with other clinical features of hypothalamic dysfunction.

Radiotherapy is an important risk factor for the development of cerebrovascular disease.[70] However, none of the studies that examined excess morbidity and mortality in patients with craniopharyngioma (including ours) observed an increased risk for cerebrovascular disease associated with radiotherapy. This indicates that other factors, like neurosurgery and metabolic disturbances due to hypothalamic damage and hypopituitarism, also contribute to the development of cerebrovascular disease in patients with craniopharyngioma. In addition, available studies may have included patients too young with a follow-up duration too short to already observe an increased risk for cerebrovascular disease associated with radiotherapy. Future studies should have a longer follow-up duration.

Patients with craniopharyngioma are at increased risk for mortality compared to patients with hypopituitarism due to other causes.[57, 60] Although the underlying reason is unknown, craniopharyngioma-specific factors (e.g. hypothalamic damage, severe hypopituitarism, a locally aggressive tumour behaviour with a high recurrence rate) are likely to be involved.[71] Future studies are needed to gain insight into this issue. Such studies should compare patients with craniopharyngioma to a control population with hypopituitarism due to other causes and should also investigate cause-specific mortality.

**KEY POINTS:**

Patients with craniopharyngioma are at increased risk for morbidity due to T2DM and cerebral infarction, as well as total mortality and mortality due circulatory and respiratory diseases.

Craniopharyngioma treatment should aim to preserve hypothalamic and pituitary functions and provide optimal endocrine care.

### The MetS and its components in patients with craniopharyngioma

As discussed above, obesity is an important long-term health condition in patients with craniopharyngioma. Obesity is often associated with other metabolic abnormalities, like those constituting the MetS.[33] In **Chapter 6**, we performed the largest study to date that investigated the MetS and its components in patients with craniopharyngioma. In a combined cohort of Dutch and Swedish patients, we examined the prevalence of and risk factors for the MetS and its components relative to the general population.

We observed the MetS and its components to be significantly more common in patients with craniopharyngioma. After a median follow-up period of 16 years, almost half of the patients with craniopharyngioma demonstrated the MetS. We identified visual impairment as the most important risk factor for the MetS. Hypothalamic damage, follow-up duration, tumour location, female sex, [90]Yttrium brachytherapy, glucocorticoid replacement therapy, and age significantly predicted components. Our results confirm previous studies that investigated the MetS in patients with craniopharyngioma.[58, 72-74]

The discussion on the increased risk for morbidity and mortality in patients with craniopharyngioma above, may also apply to the high prevalence of the MetS and its components. Visual impairment may contribute to the MetS due to a negative effect on physical activity. Several studies reported a significantly lower level of physical activity in patients with craniopharyngioma compared to age-, sex-, and body mass index-matched control subjects.[75, 76] This indicates that insufficient physical activity does not only contribute to the development of the MetS in individuals treated for a malignant tumour, but also in individuals treated for a benign neoplasm (i.e. craniopharyngioma).

Although patients with craniopharyngioma are at increased risk for mortality compared to patients with hypopituitarism due to other causes,[57, 60] and mortality in both patients with craniopharyngioma and patients with hypopituitarism due to other causes is predominantly circulatory,[71] the prevalence of the MetS has been reported to be similar.[74, 77, 78] This striking finding may be explained by the fact that studies reporting this issue investigated the MetS before commencement of growth hormone replacement therapy (GHRT). Profka et al. demonstrated that after five years of GHRT, the MetS is significantly more prevalent in patients with craniopharyngioma compared to patients

with hypopituitarism due other causes.[74] The higher prevalence of the MetS in patients with craniopharyngioma may be due to a high frequency of hypothalamic damage. Recent studies in rodents demonstrated that hypothalamic growth hormone signalling plays an important role in the central regulation of metabolism.[79, 80] Future studies that compare the prevalence of the MetS between patients with craniopharyngioma and patients with hypopituitarism due to other causes should include patients who are adequately substituted with hormone replacement therapy.

The data above suggest that the MetS may be largely responsible for the excess morbidity and mortality due to T2DM and circulatory diseases in patients with craniopharyngioma. The high prevalence of the MetS warrants regular screening and appropriate treatment. Future studies should investigate interventions that aim to reduce the prevalence of the MetS and its components. Such studies should preferably focus on obesity, since visceral adipose tissue-induced insulin resistance seems to be the principal factor resulting in the MetS and its components.[33]

**KEY POINTS:**

The MetS is significantly more common in patients with craniopharyngioma compared to the general population. After 16 years of follow-up since craniopharyngioma diagnosis, almost half of the patients demonstrate the MetS.

The high prevalence of the MetS in patients with craniopharyngioma seems to be due to hypothalamic damage and hypopituitarism, as well as visual impairment.

The MetS may be largely responsible for the excess morbidity and mortality due to T2DM and circulatory diseases in patients with craniopharyngioma.

**Bariatric surgery as an intervention for craniopharyngioma-related obesity**

As discussed above, obesity is a major problem in patients with craniopharyngioma. It contributes to the high prevalence of the MetS and subsequent excess morbidity and mortality due to T2DM and circulatory diseases, and it has been identified as the most important predictor of a worse quality of life.[44, 81-84] Treatment of obesity in patients with craniopharyngioma is difficult. Intensive lifestyle modification only slows weight gain,[85, 86] while currently available pharmacotherapies result in minimal weight loss coupled with significant side effects.[62, 87] Therefore, in **Chapter 7**, we studied bariatric surgery as a therapy for craniopharyngioma-related obesity in a combined cohort of Dutch and Swedish patients. Thereby, we performed the first matched case-control study that evaluated the efficacy and safety of two bariatric procedures (i.e. Roux-en-Y

gastric bypass and sleeve gastrectomy) in patients with craniopharyngioma. We validated our results in a meta-analysis.

After two years of follow-up, weight loss after bariatric surgery was comparable between patients with craniopharyngioma and control subjects with common obesity. Roux-en-Y gastric bypass resulted in similar weight loss, while weight loss after sleeve gastrectomy was significantly lower in patients with craniopharyngioma. Our meta-analysis confirmed these findings. Both bariatric procedures seemed safe regarding their effects on hormone replacement therapy. A previous meta-analysis evaluated weight loss after two other bariatric procedures (i.e. laparoscopic adjustable gastric banding and biliopancreatic diversion with duodenal switch).[88] Laparoscopic adjustable gastric banding did not result in significant weight loss, while weight loss after biliopancreatic diversion with duodenal switch could not be reliably analysed due to the low number of patients. Similar to our study, two other reports showed that gastric bypass and sleeve gastrectomy in patients with craniopharyngioma seemed safe regarding their effects on hormone replacement therapy.[89, 90]

The exact mechanisms by which bariatric procedures result in weight loss remain largely unknown. Alterations in eating behaviour and metabolism due to changes in gut hormone and autonomous nervous system signalling are postulated to be involved.[91] The hypothalamus plays a key role in integrating gut hormone and autonomous nervous system signalling.[92] Since patients with craniopharyngioma often demonstrate hypothalamic damage, the effectiveness of bariatric surgery has been questioned. However, as our findings indicate, weight loss after bariatric surgery may be comparable to control subjects with common obesity. This may be explained by the fact that brain circuits and gut hormone receptors responsible for the beneficial effects of bariatric procedures are not only found in the hypothalamus, but in other brain regions as well.[92, 93]

Although our results are retrospective and limited by a small study population and short duration of follow-up, they suggest that bariatric surgery, especially with Roux-en-Y gastric bypass, may be an effective and safe therapy for craniopharyngioma-related obesity. However, careful drug monitoring is still advised. Future studies are needed that prospectively evaluate the efficacy and safety of bariatric procedures in larger cohorts of patients with craniopharyngioma after a longer duration of follow-up. Such studies should preferably have a randomized controlled design, and use pharmacokinetic and pharmacodynamic parameters to investigate the effects of bariatric procedures on hormone replacement therapy. In addition, such studies should examine other potential complications of bariatric surgery, like nutrient deficiencies and surgical-related problems. Moreover, the effects of bariatric procedures on the MetS, T2DM, and cardio- and cerebrovascular disease should be investigated, as studies in the general population reported a significantly lower prevalence of these conditions after bariatric surgery.[94-97]

Another important aspect to consider in the bariatric surgical treatment of patients with craniopharyngioma is the timing of the intervention. Obesity develops predominantly during the first twelve years after craniopharyngioma treatment.[98] In this twelve years, the most significant weight gain occurs during the first year.[99] Accordingly, one might argue that early intervention with bariatric surgery may prevent severe weight gain. Thereby, it is important to consider that approximately 30% of craniopharyngiomas present in children and adolescents.[100] Although bariatric surgery has been proven to be effective in adolescents with common obesity,[101] there are considerable ethical and moral concerns.[102, 103] Currently, there is insufficient evidence to recommend bariatric surgery for obesity in paediatric patients with craniopharyngioma.

**KEY POINT:**

Bariatric surgery, especially with Roux-en-Y gastric bypass, seems to be an effective and safe therapy for craniopharyngioma-related hypothalamic obesity. However, future studies are needed to prospectively evaluate the efficacy and safety of bariatric procedures in larger cohorts of patients after a longer duration of follow-up.

### Future perspectives for patients with craniopharyngioma

As discussed above, the ideal craniopharyngioma treatment strategy should aim to preserve hypothalamic and pituitary functions and provide optimal endocrine care. Recent advances in the treatment of craniopharyngiomas (e.g. endoscopic endonasal tumour resection, proton therapy, targeted drug therapy) allow a more precise tumour treatment whereby sparing healthy surrounding tissues.[104-111] Therefore, these promising therapies may result in similar or even better treatment outcomes coupled with less long-term toxicities. However, their place in the craniopharyngioma treatment armamentarium still needs to be determined.

Glucagon-like peptide-1 (GLP-1) is one of the gut hormones responsible for weight loss after bariatric surgery.[91, 92] Recently, GLP-1 receptor agonists have become available.[112] Although these agents were originally developed and approved for the treatment of T2DM,[113] one of them (i.e. liraglutide) has now also been approved as a therapy for obesity.[114] Several case reports and series described that these agents may also induce significant weight loss in patients with craniopharyngioma.[115, 116] Pharmacotherapies based on other gut hormones (i.e. ghrelin, peptide YY, and cholecystokinin) are under development.[117-119] Future studies should determine the therapeutic potential of these promising agents that may eventually replace bariatric surgery as a therapy for craniopharyngioma-related obesity.

## CONCLUSION

To date, more than 32.5 million individuals in the world are long-term survivors of be-
nign and malignant neoplasms.[120] Due to ongoing improvements in cancer treatment
and care,[121] this number is anticipated to increase. The findings from this thesis illustrate
the importance of continuous research and follow-up care of this patient population.
Unfortunately, patients with craniopharyngioma are not included in the recently started
DCOG-LATER studies.[19] Due to the rarity of craniopharyngiomas, as well as their broad
spectrum of long-term sequelae, multidisciplinary care in expert centres and multi-
institutional research collaboration is recommended. Therefore, we were very privileged
with the international collaboration with the Sahlgrenska University Hospital in Gothen-
burg, Sweden. For future studies, these collaborations should be extended.

## REFERENCES

1. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen WQ, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP & Group CW. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2015 **385** 977-1010.

2. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, Trama A, Visser O, Brenner H, Ardanaz E, Bielska-Lasota M, Engholm G, Nennecke A, Siesling S, Berrino F, Capocaccia R & Group E-W. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. *Lancet Oncol* 2014 **15** 23-34.

3. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, Dimitrova N, Jakab Z, Kaatsch P, Lacour B, Mallone S, Marcos-Gragera R, Minicozzi P, Sanchez-Perez MJ, Sant M, Santaquilani M, Stiller C, Tavilla A, Trama A, Visser O, Peris-Bonet R & Group EW. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. *Lancet Oncol* 2014 **15** 35-47.

4. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ & Cronin KA. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, 2017.

5. Mullan F. Seasons of survival: reflections of a physician with cancer. *N Engl J Med* 1985 **313** 270-273.

6. *Institute of Medicine and National Research Council. From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington, DC: The National Academies Press, 2006.

7. Hewitt M, Weiner SL & Simone JV. In *Childhood Cancer Survivorship: Improving Care and Quality of Life*. Washington (DC), 2003.

8. Stein KD, Syrjala KL & Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer* 2008 **112** 2577-2592.

9. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W, Robison LL & Childhood Cancer Survivor S. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006 **355** 1572-1582.

10. Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, Jaspers MW, Koning CC, Oldenburger F, Langeveld NE, Hart AA, Bakker PJ, Caron HN & van Leeuwen FE. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007 **297** 2705-2715.

11. Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, Green DM, Armstrong GT, Nottage KA, Jones KE, Sklar CA, Srivastava DK & Robison LL. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA* 2013 **309** 2371-2381.

12. de Fine Licht S, Winther JF, Gudmundsdottir T, Holmqvist AS, Bonnesen TG, Asdahl PH, Tryggvadottir L, Anderson H, Wesenberg F, Malila N, Holm K, Hasle H, Olsen JH & group ALs. Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study. *Lancet* 2014 **383** 1981-1989.

13. Chao C, Xu L, Bhatia S, Cooper R, Brar S, Wong FL & Armenian SH. Cardiovascular Disease Risk Profiles in Survivors of Adolescent and Young Adult (AYA) Cancer: The Kaiser Permanente AYA Cancer Survivors Study. *J Clin Oncol* 2016 **34** 1626-1633.

14.  Smith AW, Reeve BB, Bellizzi KM, Harlan LC, Klabunde CN, Amsellem M, Bierman AS & Hays RD. Cancer, comorbidities, and health-related quality of life of older adults. *Health Care Financ Rev* 2008 **29** 41-56.

15.  Khan NF, Mant D, Carpenter L, Forman D & Rose PW. Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study. *Br J Cancer* 2011 **105 Suppl 1** S29-37.

16.  Cho H, Mariotto AB, Mann BS, Klabunde CN & Feuer EJ. Assessing non-cancer-related health status of US cancer patients: other-cause survival and comorbidity prevalence. *Am J Epidemiol* 2013 **178** 339-349.

17.  Gebauer J, Fick EM, Waldmann A, Langer T, Kreitschmann-Andermahr I, Lehnert H, Katalinic A & Brabant G. Self-reported endocrine late effects in adults treated for brain tumours, Hodgkin and non-Hodgkin lymphoma: a registry based study in Northern Germany. *Eur J Endocrinol* 2015 **173** 139-148.

18.  Armenian SH, Xu L, Ky B, Sun C, Farol LT, Pal SK, Douglas PS, Bhatia S & Chao C. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. *J Clin Oncol* 2016 **34** 1122-1130.

19.  DCOG-LATER. [SKION LATER Study].

20.  Morton LM, Onel K, Curtis RE, Hungate EA & Armstrong GT. The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. *Am Soc Clin Oncol Educ Book* 2014 e57-67.

21.  Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL & Neglia JP. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2010 **102** 1083-1095.

22.  van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, Crommelin MA, Aleman BM, Broeks A, Gospodarowicz M, Travis LB & Russell NS. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst* 2003 **95** 971-980.

23.  De Bruin ML, Sparidans J, van't Veer MB, Noordijk EM, Louwman MW, Zijlstra JM, van den Berg H, Russell NS, Broeks A, Baaijens MH, Aleman BM & van Leeuwen FE. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. *J Clin Oncol* 2009 **27** 4239-4246.

24.  Hill DA, Gilbert E, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Wiklund T, Lynch CF, Van't Veer M, Storm H, Pukkala E, Stovall M, Curtis RE, Allan JM, Boice JD & Travis LB. Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. *Blood* 2005 **106** 3358-3365.

25.  Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Wiklund T, Lynch CF, Van't Veer MB, Glimelius I, Storm H, Pukkala E, Stovall M, Curtis R, Boice JD, Jr. & Gilbert E. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA* 2003 **290** 465-475.

26.  Cooke R, Jones ME, Cunningham D, Falk SJ, Gilson D, Hancock BW, Harris SJ, Horwich A, Hoskin PJ, Illidge T, Linch DC, Lister TA, Lucraft HH, Radford JA, Stevens AM, Syndikus I, Williams MV, England, Wales Hodgkin Lymphoma Follow-up G & Swerdlow AJ. Breast cancer risk following Hodgkin lymphoma radiotherapy in relation to menstrual and reproductive factors. *Br J Cancer* 2013 **108** 2399-2406.

27.  Moskowitz CS, Chou JF, Sklar CA, Barnea D, Ronckers CM, Friedman DN, Neglia JP, Turcotte L, Howell RM, Henderson TO, Armstrong GT, Leisenring WM, Robison LL, van Leeuwen FE, Pike MC &

Oeffinger KC. Radiation-associated breast cancer and gonadal hormone exposure: a report from the Childhood Cancer Survivor Study. *Br J Cancer* 2017 **117** 290-299.

28.   National Collaborating Centre for Women's and Children's Health. Management of premature ovarian insufficiency. In *Menopause: Full Guideline*. London, 2015.

29.   van Waas M, Neggers SJ, van der Lelij AJ, Pieters R & van den Heuvel-Eibrink MM. The metabolic syndrome in adult survivors of childhood cancer, a review. *J Pediatr Hematol Oncol* 2010 **32** 171-179.

30.   de Haas EC, Oosting SF, Lefrandt JD, Wolffenbuttel BH, Sleijfer DT & Gietema JA. The metabolic syndrome in cancer survivors. *Lancet Oncol* 2010 **11** 193-203.

31.   Jung HS, Myung SK, Kim BS & Seo HG. Metabolic syndrome in adult cancer survivors: a meta-analysis. *Diabetes Res Clin Pract* 2012 **95** 275-282.

32.   Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC, Jr., International Diabetes Federation Task Force on E, Prevention, Hational Heart L, Blood I, American Heart A, World Heart F, International Atherosclerosis S & International Association for the Study of O. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009 **120** 1640-1645.

33.   Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H & Eckel RH. The metabolic syndrome. *Endocr Rev* 2008 **29** 777-822.

34.   Edwardson CL, Gorely T, Davies MJ, Gray LJ, Khunti K, Wilmot EG, Yates T & Biddle SJ. Association of sedentary behaviour with metabolic syndrome: a meta-analysis. *PLoS One* 2012 **7** e34916.

35.   He D, Xi B, Xue J, Huai P, Zhang M & Li J. Association between leisure time physical activity and metabolic syndrome: a meta-analysis of prospective cohort studies. *Endocrine* 2014 **46** 231-240.

36.   Wendel-Vos GC, Schuit AJ, Saris WH & Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol* 2003 **56** 1163-1169.

37.   Ness KK, Leisenring WM, Huang S, Hudson MM, Gurney JG, Whelan K, Hobbie WL, Armstrong GT, Robison LL & Oeffinger KC. Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer* 2009 **115** 1984-1994.

38.   Stolley MR, Restrepo J & Sharp LK. Diet and physical activity in childhood cancer survivors: a review of the literature. *Ann Behav Med* 2010 **39** 232-249.

39.   Demark-Wahnefried W, Rogers LQ, Alfano CM, Thomson CA, Courneya KS, Meyerhardt JA, Stout NL, Kvale E, Ganzer H & Ligibel JA. Practical clinical interventions for diet, physical activity, and weight control in cancer survivors. *CA Cancer J Clin* 2015 **65** 167-189.

40.   Redig AJ & Munshi HG. Care of the cancer survivor: metabolic syndrome after hormone-modifying therapy. *Am J Med* 2010 **123** 87 e81-86.

41.   Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, Panagiotakos DB & Giugliano D. Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis. *Endocrine* 2013 **44** 634-647.

42.   Westerink NL, Nuver J, Lefrandt JD, Vrieling AH, Gietema JA & Walenkamp AM. Cancer treatment induced metabolic syndrome: Improving outcome with lifestyle. *Crit Rev Oncol Hematol* 2016 **108** 128-136.

43.    Clark CC, Barnes CM, Stratton G, McNarry MA, Mackintosh KA & Summers HD. A Review of Emerging Analytical Techniques for Objective Physical Activity Measurement in Humans. *Sports Med* 2017 **47** 439-447.

44.    Kendall-Taylor P, Jonsson PJ, Abs R, Erfurth EM, Koltowska-Haggstrom M, Price DA & Verhelst J. 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** 557-567.

45.    Sughrue ME, Yang I, Kane AJ, Fang S, Clark AJ, Aranda D, Barani IJ & Parsa AT. Endocrinologic, neurologic, and visual morbidity after treatment for craniopharyngioma. *J Neurooncol* 2011 **101** 463-476.

46.    Gautier A, Godbout A, Grosheny C, Tejedor I, Coudert M, Courtillot C, Jublanc C, De Kerdanet M, Poirier JY, Riffaud L, Sainte-Rose C, Van Effenterre R, Brassier G, Bonnet F, Touraine P & Craniopharyngioma Study G. Markers of recurrence and long-term morbidity in craniopharyngioma: a systematic analysis of 171 patients. *J Clin Endocrinol Metab* 2012 **97** 1258-1267.

47.    Du C, Feng CY, Yuan XR, Liu Q, Peng ZF, Jiang XJ, Li XJ, Xiao GL, Li YF & Xiong T. Microsurgical Management of Craniopharyngiomas via a Unilateral Subfrontal Approach: A Retrospective Study of 177 Continuous Cases. *World Neurosurg* 2016 **90** 454-468.

48.    Tan TS, Patel L, Gopal-Kothandapani JS, Ehtisham S, Ikazoboh EC, Hayward R, Aquilina K, Skae M, Thorp N, Pizer B, Didi M, Mallucci C, Blair JC, Gaze MN, Kamaly-Asl I, Spoudeas H & Clayton PE. The neuroendocrine sequelae of paediatric craniopharyngioma: a 40 year meta-data analysis of 185 cases from three UK centres. *Eur J Endocrinol* 2017.

49.    Shi X, Zhou Z, Wu B, Zhang Y, Qian H, Sun Y, Yang Y, Yu Z, Tang Z & Lu S. Outcome of Radical Surgical Resection for Craniopharyngioma with Hypothalamic Preservation: A Single-Center, Retrospective Study of 1054 Patients. *World Neurosurg* 2017.

50.    Muller HL. Craniopharyngioma. *Endocr Rev* 2014 er20131115.

51.    Karavitaki N. Management of craniopharyngiomas. *J Endocrinol Invest* 2014 **37** 219-228.

52.    Schoenfeld A, Pekmezci M, Barnes MJ, Tihan T, Gupta N, Lamborn KR, Banerjee A, Mueller S, Chang S, Berger MS & Haas-Kogan D. The superiority of conservative resection and adjuvant radiation for craniopharyngiomas. *J Neurooncol* 2012 **108** 133-139.

53.    Lo AC, Howard AF, Nichol A, Sidhu K, Abdulsatar F, Hasan H & Goddard K. Long-term outcomes and complications in patients with craniopharyngioma: the british columbia cancer agency experience. *Int J Radiat Oncol Biol Phys* 2014 **88** 1011-1018.

54.    Muller HL, Emser A, Faldum A, Bruhnken G, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R & Sorensen N. Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma. *J Clin Endocrinol Metab* 2004 **89** 3298-3305.

55.    Naing NN. Easy way to learn standardization : direct and indirect methods. *Malays J Med Sci* 2000 **7** 10-15.

56.    Bulow B, Attewell R, Hagmar L, Malmstrom P, Nordstrom CH & Erfurth EM. Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumor recurrence. *J Clin Endocrinol Metab* 1998 **83** 3897-3904.

57.    Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, Sheppard MC & Stewart PM. Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. *Lancet* 2001 **357** 425-431.

58.    Pereira AM, Schmid EM, Schutte PJ, Voormolen JH, Biermasz NR, van Thiel SW, Corssmit EP, Smit JW, Roelfsema F & Romijn JA. High prevalence of long-term cardiovascular, neurological and

psychosocial morbidity after treatment for craniopharyngioma. *Clin Endocrinol (Oxf)* 2005 **62** 197-204.

59.   Crowley RK, Hamnvik OP, O'Sullivan EP, Behan LA, Smith D, Agha A & Thompson CJ. Morbidity and mortality in patients with craniopharyngioma after surgery. *Clin Endocrinol (Oxf)* 2010 **73** 516-521.

60.   Gaillard RC, Mattsson AF, Akerblad AC, Bengtsson BA, Cara J, Feldt-Rasmussen U, Koltowska-Haggstrom M, Monson JP, Saller B, Wilton P & Abs R. Overall and cause-specific mortality in GH-deficient adults on GH replacement. *Eur J Endocrinol* 2012 **166** 1069-1077.

61.   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. *J Clin Endocrinol Metab* 2015 **100** 467-474.

62.   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** 1774-1797.

63.   Higham CE, Johannsson G & Shalet SM. Hypopituitarism. *Lancet* 2016 **388** 2403-2415.

64.   Sullivan SD, Sarrel PM & Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. *Fertil Steril* 2016 **106** 1588-1599.

65.   Puget S, Garnett M, Wray A, Grill J, Habrand JL, Bodaert N, Zerah M, Bezerra M, Renier D, Pierre-Kahn A & Sainte-Rose C. Pediatric craniopharyngiomas: classification and treatment according to the degree of hypothalamic involvement. *J Neurosurg* 2007 **106** 3-12.

66.   Van Gompel JJ, Nippoldt TB, Higgins DM & Meyer FB. Magnetic resonance imaging-graded hypothalamic compression in surgically treated adult craniopharyngiomas determining postoperative obesity. *Neurosurg Focus* 2010 **28** E3.

67.   Muller HL, Gebhardt U, Teske C, Faldum A, Zwiener I, Warmuth-Metz M, Pietsch T, Pohl F, Sorensen N, Calaminus G & Study Committee of K. Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. *Eur J Endocrinol* 2011 **165** 17-24.

68.   Mallucci C, Pizer B, Blair J, Didi M, Doss A, Upadrasta S, Newman W, Avula S & Pettorini B. Management of craniopharyngioma: the Liverpool experience following the introduction of the CCLG guidelines. Introducing a new risk assessment grading system. *Childs Nerv Syst* 2012 **28** 1181-1192.

69.   Mortini P, Gagliardi F, Bailo M, Spina A, Parlangeli A, Falini A & Losa M. Magnetic resonance imaging as predictor of functional outcome in craniopharyngiomas. *Endocrine* 2016 **51** 148-162.

70.   Plummer C, Henderson RD, O'Sullivan JD & Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. *Stroke* 2011 **42** 2410-2418.

71.   Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, Bates AS & Stewart PM. Mortality in patients with pituitary disease. *Endocr Rev* 2010 **31** 301-342.

72.   Holmer H, Ekman B, Bjork J, Nordstom CH, Popovic V, Siversson A & Erfurth EM. Hypothalamic involvement predicts cardiovascular risk in adults with childhood onset craniopharyngioma on long-term GH therapy. *Eur J Endocrinol* 2009 **161** 671-679.

73.   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** 364-370.

74.   Profka E, Giavoli C, Bergamaschi S, Ferrante E, Malchiodi E, Sala E, Verrua E, Rodari G, Filopanti M, Beck-Peccoz P & Spada A. Analysis of short- and long-term metabolic effects of growth hormone

replacement therapy in adult patients with craniopharyngioma and non-functioning pituitary adenoma. *J Endocrinol Invest* 2015 **38** 413-420.

75. 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** 5227-5231.

76. Piguel X, Abraham P, Bouhours-Nouet N, Gatelais F, Dufresne S, Rouleau S & Coutant R. Impaired aerobic exercise adaptation in children and adolescents with craniopharyngioma is associated with hypothalamic involvement. *Eur J Endocrinol* 2012 **166** 215-222.

77. Attanasio AF, Mo D, Erfurth EM, Tan M, Ho KY, Kleinberg D, Zimmermann AG, Chanson P & International Hypopituitary Control Complications Study Advisory B. Prevalence of metabolic syndrome in adult hypopituitary growth hormone (GH)-deficient patients before and after GH replacement. *J Clin Endocrinol Metab* 2010 **95** 74-81.

78. Verhelst J, Mattsson AF, Luger A, Thunander M, Goth MI, Koltowska-Haggstrom M & Abs R. Prevalence and characteristics of the metabolic syndrome in 2479 hypopituitary patients with adult-onset GH deficiency before GH replacement: a KIMS analysis. *Eur J Endocrinol* 2011 **165** 881-889.

79. Furigo IC, Metzger M, Teixeira PD, Soares CR & Donato J, Jr. Distribution of growth hormone-responsive cells in the mouse brain. *Brain Struct Funct* 2017 **222** 341-363.

80. Cady G, Landeryou T, Garratt M, Kopchick JJ, Qi N, Garcia-Galiano D, Elias CF, Myers MG, Jr., Miller RA, Sandoval DA & Sadagurski M. Hypothalamic growth hormone receptor (GHR) controls hepatic glucose production in nutrient-sensing leptin receptor (LepRb) expressing neurons. *Mol Metab* 2017 **6** 393-405.

81. Muller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, Korinthenberg R, Bettendorf M, Kuhl J, Gutjahr P, Sorensen N & Calaminus G. Obesity after childhood craniopharyngioma--German multicenter study on pre-operative risk factors and quality of life. *Klin Padiatr* 2001 **213** 244-249.

82. Muller HL, Faldum A, Etavard-Gorris N, Gebhardt U, Oeverink R, Kolb R & Sorensen N. Functional capacity, obesity and hypothalamic involvement: cross-sectional study on 212 patients with childhood craniopharyngioma. *Klin Padiatr* 2003 **215** 310-314.

83. Patel KS, Raza SM, McCoul ED, Patrona A, Greenfield JP, Souweidane MM, Anand VK & Schwartz TH. Long-term quality of life after endonasal endoscopic resection of adult craniopharyngiomas. *J Neurosurg* 2015 **123** 571-580.

84. Yano S, Kudo M, Hide T, Shinojima N, Makino K, Nakamura H & Kuratsu J. Quality of Life and Clinical Features of Long-Term Survivors Surgically Treated for Pediatric Craniopharyngioma. *World Neurosurg* 2016 **85** 153-162.

85. 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** 1768-1774.

86. Steele CA, Cuthbertson DJ, MacFarlane IA, Javadpour M, Das KS, Gilkes C, Wilding JP & Daousi C. Hypothalamic obesity: prevalence, associations and longitudinal trends in weight in a specialist adult neuroendocrine clinic. *Eur J Endocrinol* 2013 **168** 501-507.

87. Wang KW, Chau R, Fleming A, Banfield L, Singh SK, Johnston DL, Zelcer SM, Rassekh SR, Burrow S, Valencia M, de Souza RJ, Thabane L & Samaan MC. The effectiveness of interventions to treat hypothalamic obesity in survivors of childhood brain tumours: a systematic review. *Obes Rev* 2017.

88. Bretault M, Boillot A, Muzard L, Poitou C, Oppert JM, Barsamian C, Gatta B, Muller H, Weismann D, Rottembourg D, Inge T, Veyrie N, Carette C & Czernichow S. Clinical review: Bariatric surgery

following treatment for craniopharyngioma: a systematic review and individual-level data meta-analysis. *J Clin Endocrinol Metab* 2013 **98** 2239-2246.

89.  Wolf P, Winhofer Y, Smajis S, Kruschitz R, Schindler K, Gessl A, Riedl M, Vila G, Raber W, Langer F, Prager G, Ludvik B, Luger A & Krebs M. Hormone Substitution after Gastric Bypass Surgery in Patients with Hypopituitarism Secondary to Craniopharyngioma. *Endocr Pract* 2016.

90.  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** 95-99.

91.  Madsbad S, Dirksen C & Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. *Lancet Diabetes Endocrinol* 2014 **2** 152-164.

92.  Rao RS. Bariatric surgery and the central nervous system. *Obes Surg* 2012 **22** 967-978.

93.  Hao Z, Mumphrey MB, Morrison CD, Munzberg H, Ye J & Berthoud HR. Does gastric bypass surgery change body weight set point? *Int J Obes Suppl* 2016 **6** S37-S43.

94.  Shuai X, Tao K, Mori M & Kanda T. Bariatric surgery for metabolic syndrome in obesity. *Metab Syndr Relat Disord* 2015 **13** 149-160.

95.  Sjostrom L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. *J Intern Med* 2013 **273** 219-234.

96.  Arterburn DE & Courcoulas AP. Bariatric surgery for obesity and metabolic conditions in adults. *BMJ* 2014 **349** g3961.

97.  Puzziferri N, Roshek TB, 3rd, Mayo HG, Gallagher R, Belle SH & Livingston EH. Long-term follow-up after bariatric surgery: a systematic review. *JAMA* 2014 **312** 934-942.

98.  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** 1029-1038.

99.  Roth CL, Eslamy H, Werny D, Elfers C, Shaffer ML, Pihoker C, Ojemann J & Dobyns WB. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. *Obesity (Silver Spring)* 2015 **23** 1226-1233.

100.  Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F & Bruner JM. The descriptive epidemiology of craniopharyngioma. *J Neurosurg* 1998 **89** 547-551.

101.  Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmrath MA, Brandt ML, Harmon CM, Zeller MH, Chen MK, Xanthakos SA, Horlick M, Buncher CR & Teen LC. Weight Loss and Health Status 3 Years after Bariatric Surgery in Adolescents. *N Engl J Med* 2016 **374** 113-123.

102.  Hofmann B. Bariatric surgery for obese children and adolescents: a review of the moral challenges. *BMC Med Ethics* 2013 **14** 18.

103.  Beamish AJ & Reinehr T. Should bariatric surgery be performed in adolescents? *Eur J Endocrinol* 2017 **176** D1-D15.

104.  Liu JK, Sevak IA, Carmel PW & Eloy JA. Microscopic versus endoscopic approaches for craniopharyngiomas: choosing the optimal surgical corridor for maximizing extent of resection and complication avoidance using a personalized, tailored approach. *Neurosurg Focus* 2016 **41** E5.

105.  Wannemuehler TJ, Rubel KE, Hendricks BK, Ting JY, Payner TD, Shah MV & Cohen-Gadol AA. Outcomes in transcranial microsurgery versus extended endoscopic endonasal approach for primary resection of adult craniopharyngiomas. *Neurosurg Focus* 2016 **41** E6.

106.  Moussazadeh N, Prabhu V, Bander ED, Cusic RC, Tsiouris AJ, Anand VK & Schwartz TH. Endoscopic endonasal versus open transcranial resection of craniopharyngiomas: a case-matched single-institution analysis. *Neurosurg Focus* 2016 **41** E7.

107. Conroy R, Gomes L, Owen C, Buchsbaum J & Ahern V. Clinical equipoise: Protons and the child with craniopharyngioma. *J Med Imaging Radiat Oncol* 2015 **59** 379-385.

108. Martinez-Gutierrez JC, D'Andrea MR, Cahill DP, Santagata S, Barker FG, 2nd & Brastianos PK. Diagnosis and management of craniopharyngiomas in the era of genomics and targeted therapy. *Neurosurg Focus* 2016 **41** E2.

109. Robinson LC, Santagata S & Hankinson TC. Potential evolution of neurosurgical treatment paradigms for craniopharyngioma based on genomic and transcriptomic characteristics. *Neurosurg Focus* 2016 **41** E3.

110. Apps JR & Martinez-Barbera JP. Molecular pathology of adamantinomatous craniopharyngioma: review and opportunities for practice. *Neurosurg Focus* 2016 **41** E4.

111. Brastianos PK, Shankar GM, Gill CM, Taylor-Weiner A, Nayyar N, Panka DJ, Sullivan RJ, Frederick DT, Abedalthagafi M, Jones PS, Dunn IF, Nahed BV, Romero JM, Louis DN, Getz G, Cahill DP, Santagata S, Curry WT, Jr. & Barker FG, 2nd. Dramatic Response of BRAF V600E Mutant Papillary Craniopharyngioma to Targeted Therapy. *J Natl Cancer Inst* 2016 **108**.

112. Davidson MB, Bate G & Kirkpatrick P. Exenatide. *Nat Rev Drug Discov* 2005 **4** 713-714.

113. Lovshin JA & Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. *Nat Rev Endocrinol* 2009 **5** 262-269.

114. Nuffer WA & Trujillo JM. Liraglutide: A New Option for the Treatment of Obesity. *Pharmacotherapy* 2015 **35** 926-934.

115. 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** 635-637.

116. 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** 699-706.

117. Barnett BP, Hwang Y, Taylor MS, Kirchner H, Pfluger PT, Bernard V, Lin YY, Bowers EM, Mukherjee C, Song WJ, Longo PA, Leahy DJ, Hussain MA, Tschop MH, Boeke JD & Cole PA. Glucose and weight control in mice with a designed ghrelin O-acyltransferase inhibitor. *Science* 2010 **330** 1689-1692.

118. Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD & Bloom SR. Gut hormone PYY(3-36) physiologically inhibits food intake. *Nature* 2002 **418** 650-654.

119. Irwin N, Frizelle P, Montgomery IA, Moffett RC, O'Harte FPM & Flatt PR. Beneficial effects of the novel cholecystokinin agonist (pGlu-Gln)-CCK-8 in mouse models of obesity/diabetes. *Diabetologia* 2012 **55** 2747-2758.

120. Bray F, Ren JS, Masuyer E & Ferlay J. GLOBOCAN 2012 v1.0, Cancer Prevalence Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer, 2013.

121. Milestones in Cancer Research and Discovery. National Cancer Institute (NCI).

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# Chapter 9

## Summary en samenvatting

## SUMMARY

Cancer survival increased substantially during the past decades. Accordingly, long-term consequences of cancer and its treatment have become increasingly important. A high prevalence of chronic health effects has been reported in both childhood and adult cancer survivors (**Chapter 1**). The aim of this thesis was to examine long-term endocrine and metabolic conditions, as well as their determinants in patients treated for cancer with a special focus on patients treated for craniopharyngioma.

### Long-term endocrine and metabolic consequences of cancer and its treatment

The development of a subsequent neoplasm is an important long-term health condition in cancer survivors. We reviewed the literature on risk factors for subsequent endocrine-related cancer in childhood cancer survivors. Thereby, we focused on secondary tumors of the breast and thyroid (**Chapter 2**). We identified the potential harmful effects of estrogen-progestin replacement therapy on radiation-induced breast cancer development as the most important area for future research.

The metabolic syndrome is also a common long-term health effect in cancer survivors. An unhealthy lifestyle with insufficient physical activity seems an important risk factor. Therefore, we studied daily life physical activity in survivors of nephroblastoma and neuroblastoma relative to a control group not treated for cancer (**Chapter 3**). We observed a significantly lower level of physical activity in male neuroblastoma survivors compared to male control subjects. Female neuroblastoma survivors and male and female nephroblastoma survivors showed similar physical activity levels compared to control subjects.

### Long-term endocrine and metabolic consequences in patients with craniopharyngioma

Craniopharyngiomas are benign intracranial neoplasms that affect children and adults. They may cause significant long-term tumor- and treatment-related morbidities. We studied long-term sequelae of various initial craniopharyngioma treatment strategies in both patients with childhood- and adult-onset craniopharyngioma (**Chapter 4**). Pituitary hormone deficiencies, visual impairment, and obesity were the most common long-term health conditions. [90]Yttrium brachytherapy and cyst drainage resulted in similar long-term health effects as gross total resection and subtotal resection with or without radiotherapy. Recurrence-free survival was significantly lower after cyst drainage. Patients with childhood-onset disease showed a significantly higher prevalence of pituitary hormone deficiencies, morbid obesity, epilepsy, and psychiatric conditions compared to patients with adult-onset disease.

In addition, we investigated morbidity and mortality in Dutch and Swedish patients with craniopharyngioma relative to the general population (**Chapter 5**). We observed

excess morbidity due to type 2 diabetes mellitus and cerebral infarction, as well as excess total mortality and mortality due to circulatory and respiratory diseases. We identified hypothalamic and pituitary damage as the principal determinants.

### The metabolic syndrome and its components in patients with craniopharyngioma

We studied the metabolic syndrome and its components in Dutch and Swedish patients with craniopharyngioma (**Chapter 6**). The metabolic syndrome and its components were significantly more common in patients with craniopharyngioma compared to the general population. In addition to hypothalamic and pituitary damage, visual impairment was identified as an important risk factor. Excess morbidity and mortality in patients with craniopharyngioma may be mainly driven by the metabolic syndrome.

### Bariatric surgery as an intervention for craniopharyngioma-related obesity

We investigated the efficacy and safety of bariatric surgery in Dutch and Swedish patients with craniopharyngioma relative to matched control subjects with common obesity (**Chapter 7**). After two years of follow-up, weight loss was comparable between patients with craniopharyngioma and control subjects with common obesity. Roux-en-Y gastric bypass, but not sleeve gastrectomy, resulted in similar weight loss. Both bariatric procedures seemed safe regarding their effects on hormone replacement therapy.

### Conclusion and future perspectives

Not only patients with a malignant tumor, but also patients with a benign neoplasm (i.e. craniopharyngioma) are at risk for long-term tumor- and treatment-related endocrine and metabolic conditions (**Chapter 8**). Due to the rarity of a disease like craniopharyngioma, centralization of care is recommended, as well as multi-institutional collaboration in research. Our international collaboration with the Sahlgrenska University Hospital in Gothenburg, Sweden, should be extended for future studies.

## SAMENVATTING

De overleving van kanker is de afgelopen decennia sterk verbeterd. Hierdoor wordt er meer aandacht besteed aan de lange termijn gevolgen van kanker en de bijbehorende behandeling. Eerdere onderzoeken hebben aangetoond dat overlevenden van kanker vaak last hebben van aandoeningen die een laat gevolg zijn van de eerdere kanker en bijbehorende behandeling (**Hoofdstuk 1**). Het doel van dit proefschrift was om (risicofactoren voor) endocriene en metabole lange termijn gevolgen van kanker en de behandeling van kanker vast te stellen. Hierbij werd speciaal aandacht besteed aan mensen met een craniopharyngioom.

### Endocriene en metabole gevolgen van kanker en de behandeling van kanker

Een belangrijk lange termijn gevolg van de behandeling van kanker is het ontstaan van nieuwe tumoren. Wij hebben een overzichtsartikel gemaakt waarin wij risicofactoren beschrijven voor het ontstaan van nieuwe tumoren bij overlevenden van kinderkanker (**Hoofdstuk 2**). Hierbij hebben wij speciaal aandacht besteed aan borstkanker en schildklierkanker. Uit onze studie bleek dat er meer onderzoek nodig is naar het mogelijk risicoverhogend effect van hormonale suppletietherapie op borstkanker bij vrouwen die bestraald zijn op de borstregio.

Het metabool syndroom is een vaak voorkomende aandoening bij overlevenden van kanker. Een ongezonde levensstijl met een gebrek aan lichamelijke activiteit lijkt een belangrijke risicofactor. Daarom hebben wij lichamelijke activiteit onderzocht bij mensen die op de kinderleeftijd zijn behandeld voor een nier- of bijniertumor (**Hoofdstuk 3**). Mannen die voor een bijniertumor behandeld zijn, bleken significant minder actief dan controlepersonen. Vrouwen die voor een bijniertumor behandeld zijn, evenals mannen en vrouwen die voor een niertumor behandeld zijn, bleken even actief als controlepersonen.

### Endocriene en metabole gevolgen van craniopharyngiomen

Craniopharyngiomen zijn goedaardige hersentumoren die zowel bij kinderen als volwassenen voorkomen. Lange termijn problemen veroorzaakt door de tumor en bijbehorende behandeling komen vaak voor. Wij hebben lange termijn gevolgen van verschillende behandelingen van craniopharyngiomen onderzocht. Tevens hebben wij deze lange termijn gevolgen vergeleken tussen mensen die zich als kind en volwassene presenteerden met een craniopharyngioom (**Hoofdstuk 4**). In ons onderzoek waren hormoonuitval, problemen met het zicht en obesitas de meest voorkomende lange termijn problemen. Behandeling middels operatie, bestraling, [90]Yttrium brachytherapie en cysteaspiratie resulteerden in dezelfde lange termijn problemen. De kans op een recidieftumor was significant groter na behandeling met cysteaspiratie. Mensen die op

de kinderleeftijd gediagnosticeerd zijn met een craniopharyngioom hadden significant vaker last van hormoonuitval, morbide obesitas, epilepsie en psychiatrische aandoeningen.

Ook hebben wij lange termijn problemen vergeleken tussen mensen die behandeld zijn voor een craniopharyngioom en de algemene bevolking (**Hoofdstuk 5**). Mensen die behandeld zijn voor een craniopharyngioom hadden significant vaker last van ouderdomssuikerziekte en herseninfarcten. Ook stierven zij significant vaker aan cardio- en cerebrovasculaire, alsmede respiratoire aandoeningen. Schade aan de hypothalamus en hypofyse bleek de belangrijkste risicofactor voor morbiditeit en mortaliteit.

### Het metabool syndroom en zijn componenten bij craniopharyngioompatiënten

Wij hebben het metabool syndroom en zijn componenten onderzocht bij mensen die behandeld zijn voor een craniopharyngioom (**Hoofdstuk 6**). Het metabool syndroom en zijn componenten kwamen significant vaker voor in vergelijking met de algemene bevolking. Naast schade aan de hypothalamus en hypofyse bleek een verminderd zicht een belangrijke risicofactor voor het metabool syndroom. Het metabool syndroom lijkt een belangrijke oorzaak te zijn voor het vaker voorkomen van morbiditeit en mortaliteit bij mensen met een craniopharyngioom.

### Bariatrische chirurgie als behandeling van obesitas bij craniopharyngioompatiënten

Hypothalame schade is de belangrijkste oorzaak van obesitas bij mensen met een craniopharyngioom. Hierdoor is het bijzonder moeilijk om af te vallen middels een dieet en lichamelijke activiteit. Medicijnen die gewichtsverlies bevorderen zijn ook niet effectief. Daarom hebben wij de effectiviteit en veiligheid van bariatrische chirurgie onderzocht (**Hoofdstuk 7**). Twee jaar na bariatrische chirurgie middels een "Roux-en-Y gastric bypass" bleken mensen met een craniopharyngioom even veel af te vallen als controlepersonen zonder een craniopharyngioom. Het gewichtsverlies na een "sleeve gastrectomy" was significant minder bij patiënten met een craniopharyngioom. Beide operaties bleken veilig betreffende hun effecten op hormonale suppletietherapie.

### Conclusie en aanbevelingen voor toekomstig onderzoek

Endocriene en metabole lange termijn gevolgen van kanker en de behandeling van kanker komen vaak voor, zowel bij mensen met een maligne als benigne tumor (**Hoofdstuk 8**). Omdat craniopharyngiomen zeldzaam zijn, zijn centralisatie van zorg en multi-institutionele samenwerking in onderzoek onontbeerlijk. Daarom zijn wij voor dit proefschrift een samenwerkingsverband aangegaan met de Sahlgrenska universiteit in Göteborg, Zweden. Voor toekomstig onderzoek dient deze samenwerking te worden uitgebreid.

# Chapter 10

## About the author

## CURRICULUM VITAE

Mark Wijnen was born on June 16th 1988 in Vlaardingen, the Netherlands. After he graduated from high school in 2007 (Groen van Prinstererlyceum, Vlaardingen), he studied medicine at the Erasmus University Rotterdam, from which he graduated *cum laude* in 2013. During medical school, he performed research on long-term consequences of childhood cancer treatment at the Department of Paediatric Oncology/Haematology (Professor Van den Heuvel-Eibrink). Subsequently, he started his PhD training in March 2014, which was a joint project between the Department of Medicine – Endocrinology/Pituitary Centre Rotterdam (Professor Van der Lelij and Doctor Neggers) and the Department of Paediatric Oncology/Haematology (Professor Van den Heuvel-Eibrink). The results of his PhD training are presented in this thesis. During his training, he has received several poster and travel awards. Besides his research, he has worked as a physician at the Late Effects clinic of the Erasmus University Medical Centre, where he treated adult survivors of childhood cancer for long-term complications of their prior treatment. After finishing his PhD training in September 2017, he started his traineeship in internal medicine at the Reinier de Graaf Gasthuis in Delft under supervision of Doctor Boom.

**LIST OF PUBLICATIONS**

1.  **Wijnen M**, Alders M, Zwaan CM, Wagner A, van den Heuvel-Eibrink MM. KCNQ1OT1 hypomethylation: a novel disguised genetic predisposition in sporadic pediatric adrenocortical tumors? *Pediatr Blood Cancer. 2012 Sep;59(3):565-6. doi: 10.1002/pbc.23398.*

2.  van Waas M, **Wijnen M**, Hartman A, de Vries AC, Pieters R, Neggers SJCMM, van den Heuvel-Eibrink MM. Daily life physical activity in long-term survivors of nephroblastoma and neuroblastoma. *J Pediatr Hematol Oncol. 2013 Jul;35(5):361-5. doi: 10.1097/MPH.0b013e31827e8fb9.*

3.  **Wijnen M**, van den Heuvel-Eibrink MM, Medici M, Peeters RP, van der Lelij AJ, Neggers, SJCMM. Risk factors for subsequent endocrine-related cancer in childhood cancer survivors. *Endocr Relat Cancer. 2016 Jun;23(6):R299-321. doi: 10.1530/ERC-16-0113.*

4.  **Wijnen M**, Olsson DS, van den Heuvel-Eibrink MM, Wallenius V, Janssen JAMJL, Delhanty PJD, van der Lelij AJ, Johannsson G, Neggers SJCMM. 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 Feb;41(2):210-216. doi: 10.1038/ijo.2016.195.*

5.  **Wijnen M**, van den Heuvel-Eibrink MM, Janssen JAMJL, Catsman-Berrevoets CE, Michiels EMC, van Veelen-Vincent MLC, Dallenga AHG, van den Berge JH, van Rij CM, van der Lelij AJ, Neggers SJCMM. Very long-term sequelae of craniopharyngioma. *Eur J Endocrinol. 2017 Jun;176(6):755-767. doi: 10.1530/EJE-17-0044.*

6.  **Wijnen M**, Olsson DS, van den Heuvel-Eibrink MM, Hammarstrand C, Janssen JAMJL, van der Lelij AJ, Johannsson G, Neggers SJCMM. The metabolic syndrome and its components in 178 patients treated for craniopharyngioma after 16 years of follow-up. *Eur J Endocrinol. 2018 Jan; 178(1):11-22. doi: 10.1530/EJE-17-0387.*

7.  **Wijnen M**, Olsson DS, van den Heuvel-Eibrink MM, Hammarstrand C, Janssen JAMJL, van der Lelij AJ, Johannsson G, Neggers SJCMM. Excess morbidity and mortality in patients with craniopharyngioma: a hospital-based retrospective cohort study. *Eur J Endocrinol. 2018 Jan; 178(1):95-104. doi: 10.1530/EJE-17-0707.*

8.  Hartman A, Pluijm SMF, **Wijnen M**, Neggers SJCMM, Clemens E, Pieters R, van den Heuvel-Eibrink MM. Health-related fitness in very long-term survivors of childhood cancer: a case-control study. *Pediatr Blood Cancer. 2018 Apr; 65(4):e26907. doi: 10.1002/pbc.26907.*

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| | Year | ECTS |
|---|---|---|
| **General courses** | | |
| Basic Course for Clinical Investigators (BROK) | 2014 | 2.0 |
| Research Integrity Course | 2015 | 0.3 |
| Biostatistical Methods I: Basic Principles, part A (CC02a) | 2016 | 2.0 |
| | | |
| **Research skills** | | |
| Weekly research meeting Endocrinology Laboratory | 2014-2017 | 4.5 |
| Weekly research meeting Paediatric Oncology/Haematology | 2014-2015 | 1.5 |
| Weekly research meeting Quality of Life and Toxicity of Care working group | 2014-2016 | 3.0 |
| Weekly research meeting Late Effects of Childhood Cancer Study | 2015-2017 | 3.0 |
| | | |
| **Seminars and workshops** | | |
| Sophia Research Day (Rotterdam, the Netherlands) | 2014 | 0.3 |
| Dutch Oncology Society (NVvO) Milestone Day (Amsterdam, the Netherlands) | 2014 | 0.3 |
| Dutch Childhood Oncology Group/Princes Maxima Centre Retreat (Utrecht, the Netherlands) | 2015 | 0.3 |
| Endocrine Retreat (Rotterdam, the Netherlands) – Oral presentation | 2015 | 1.3 |
| Thyroid Nodule and Thyroid Cancer Symposium (Rotterdam, the Netherlands) | 2015 | 0.1 |
| Pituitary Centre Rotterdam: 10-year anniversary symposium (Rotterdam, the Netherlands) – Oral presentation | 2017 | 1.3 |
| | | |
| **National and international conferences** | | |
| European Symposium on Late Complications after Childhood Cancer (Amsterdam, the Netherlands) – Poster presentation | 2011 | 1.0 |
| European Young Endocrine Scientists Conference (Rotterdam, the Netherlands) | 2013 | 0.5 |
| European Congress of Endocrinology (Wroclaw, Poland) | 2014 | 0.5 |
| European Symposium on Late Complications after Childhood Cancer (Edinburgh, Scotland) | 2014 | 0.5 |

| | | |
|---|---|---|
| European Young Endocrine Scientists Conference<br>(Belgrade, Serbia) – Oral presentation | 2014 | 1.5 |
| Aspiring to Excellence: Pituitary Expert Forum<br>(Vienna, Austria) – Poster presentation | 2014 | 1.0 |
| 14th International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer<br>(Arlington, United States of America) – Poster presentation | 2015 | 1.0 |
| Annual Congress of the International Society of Paediatric Oncology<br>(Dublin, Ireland) – Poster presentation | 2016 | 1.0 |
| 8th International Congress of the Growth Hormone Research and Insulin-like Growth Factor Research (IGF) Societies<br>(Tel Aviv, Israel) – Poster presentation | 2016 | 1.0 |

**Clinical meetings and participation**

| | | |
|---|---|---|
| Outpatient clinic for long-term complications of childhood cancer treatment | 2014-2017 | 40.0 |
| Weekly grand round of the endocrinology department | 2014-2017 | 4.5 |

**Teaching activities**

| | | |
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| Skills training first year medical students<br>*Subject: Thyroid*<br>(Erasmus University Rotterdam, Rotterdam, the Netherlands) | 2016-2017 | 2.0 |
| Basic course endocrinology for nurses<br>*Subject: Hypothalamus and pituitary*<br>(Radboud University – Health Academy, Nijmegen, the Netherlands) | 2016 | 1.0 |

**Grants writing**

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| Very long-term sequelae of childhood-onset craniopharyngioma: a comparison with adult-onset disease including $^{90}$Yttrium brachytherapy and stereotactic radiotherapy related complications | 2014 | 10.0 |

**Awards**

| | | |
|---|---|---|
| Gerrit Jan Mulder travel award<br>*European Symposium on Late Complications after Childhood Cancer*<br>*(Amsterdam, the Netherlands)* | 2011 | |
| Commended Young Investigator poster award<br>*Aspiring to Excellence: Pituitary Expert Forum*<br>*(Vienna, Austria)* | 2014 | |
| GRS-IGF travel award<br>*8th International Congress of the GRS and IGF Society*<br>*(Tel Aviv, Israel)* | 2016 | |
| Top Downloaded Article Endocrine-Related Cancer<br>*Risk factors for subsequent endocrine-related cancer in childhood cancer survivors* | 2017 | |

**Other**

| | | |
|---|---|---|
| Peer-review for *Endocrinology, Diabetes and Metabolism Case Reports* | 2017 | 0.3 |
| Peer-review for *Clinical Endocrinology* | 2017 | 0.3 |

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