KU LEUVEN

FACULTY OF MEDICINE

Radiotherapy-induced effects on the HPA-axis in children with a brain tumour

Master Thesis proposed to achieve the degree of master in medicine by

Eric VLEESHOUWERS

Unit: Faculty of Medicine

Departement: Pediatrics

Promotor: Charlotte SLEURS
Promotor: Prof. dr. Anne UYTTEBROECK

Leuven, 2019-2020

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1. COVER LETTER

Dear members of the editorial board,

I, hereby, wish to present to you my new manuscript, entitled 'Radiotherapy-induced effects on the HPA axis in children with a brain tumour', for publication in your esteemed journal.

Major advances in cancer treatment modalities during the last decade have significantly increased survival rates in children diagnosed with a brain tumor. This raised concerns regarding late adverse effects of cancer treatment and their impact on functional outcomes and quality of life, including endocrine effects. I withhold a special focus on radiotherapy-induced effects of the hypothalamic-pituitary-adrenal axis.

Various articles have already outlined one or more of these effects. However, to the best of my knowledge, a complete overview of al sub-axes of the HPA axis that were affected by radiotherapy was missing to date. We tried to realize this, screening the Pubmed/Medline database using a comprehensive search algorithm. After systematically filtering the results, 23 qualitative articles were included for analysis.

Significant findings were achieved regarding the different sub-axes. In general, anterior pituitary hormones presented to be frequently involved, especially growth hormone. Posterior pituitary hormone deficiencies were rather rare. Advances in radiotherapeutic treatment modalities appear promising in reducing radiotherapeutic effects on the hypothalamic-pituitary-adrenal axis, but need further long-term investigation.

I sincerely believe that this article reports a relevant overview on radiotherapy-induced HPA axis disorders. Also, it could be of relevance regarding future radiotherapeutic directions and future research articles to extensively evaluate a hopefully decreased radiotherapy induced toxicity to the hypothalamic-pituitary-adrenal axis.

The study was approved by the Ethics Committee of University Hospital Leuven, Belgium. The manuscript was not published, nor under editorial review for publication elsewhere. I also declare that there was no funding for this research, nor where there any other conflicts of interest.

I hope you too appreciate and enjoy reading the manuscript and consider it for publication in your journal.

Yours sincerely,

Eric Vleeshouwers

2. ABSTRACT

Background: Incidence rates of brain and other nervous system tumours in children have been stable over the last few years with a 5-year survival of approximately 80%. However, this withholds the disadvantage of long-term adverse effects of cancer treatment and their impact on quality of life, including endocrine effects.
The purpose of this systematic review was to synthesize the current evidence of radiotherapy induced effects on the hypothalamic-pituitary-adrenal axis in children diagnosed with a brain tumour.

Methods: The PUBMED/Medline database was screened for relevant articles using the following search algorithm: ("Infant"[Mesh] OR "Adolescent"[Mesh] OR "Child"[Mesh]) AND ("Hypothalamo-Hypophyseal System"[Mesh] OR "Adrenal Glands"[Mesh] OR "Pituitary Gland"[Mesh]) AND ("Brain Neoplasms"[Mesh]) AND ("Therapeutics"[Mesh]. Articles were systematically selected based on inclusion/exclusion criteria. Data were extracted using a standardized data extraction table.

Results: The literature search strategy returned 539 articles, of which we retained 23 articles for qualitative analysis.
In general, prevalence, severity, and time to onset of hypothalamic-pituitary-adrenal axis disorders are related to the total radiation dose and fractioning, age at time of diagnosis, age at start of radiotherapy and to follow-up duration.
The most common hypothalamic-pituitary-adrenal axis disorder is growth hormone deficiency(12.5-100%), followed by central adrenal insufficiency(0-43%), central hypothyroidism(0-67%), hypogonadotropic hypogonadism(0-20.4%), precocious puberty(4.6-26%), hyperprolactinemia(0-57%) and, rather uncommon, central diabetes insipidus(0-10.5%). Incidence rates of central hypothyroidism, hypogonadotropic hypogonadism, as well as a greater mean height were significantly lower among patients treated with proton beam radiation therapy.

Conclusion: Radiotherapy induces a broad range of hypothalamic-pituitary-adrenal axis deficiencies in childhood brain tumor survivors. Anterior pituitary hormones presented to be frequently involved, especially growth hormone. Posterior pituitary hormone deficiencies were rather rare.
Advances in radiotherapeutic treatment modalities appear promising in reducing radiotherapeutic effects on the hypothalamic-pituitary-adrenal axis, but need further long-term investigation.

3. NEDERLANDSTALIGE SAMENVATTING

Achtergrond: Incidentie van kinderen met een hersen- of centraal zenuwstelseltumor is de laatste jaren stabiel gebleven met een 5-jaarsoverleving van ongeveer 80%. Deze kinderen kampen echter met de nadelige effecten van hun behandeling, die een belangrijke impact hebben op de levenskwaliteit. Het doel van deze systematische review is om een overzicht te geven van de huidige evidentie rond de invloed van radiotherapie op de hypothalamus-hypofyse-bijnier-as bij kinderen met een hersentumor.

Methoden: PUBMED/Medline database werd doorzocht naar relevante artikels. Er werd gebruik gemaakt van het volgende zoekalgoritme: ("Infant"[Mesh] OR "Adolescent"[Mesh] OR "Child"[Mesh]) AND ("Hypothalamo-Hypophyseal System"[Mesh] OR "Adrenal Glands"[Mesh] OR "Pituitary Gland"[Mesh]) AND ("Brain Neoplasms"[Mesh]) AND ("Therapeutics"[Mesh]). De artikels werden systematisch geselecteerd op basis van inclusie- en exclusiecriteria. De gegevens werden geëxtraheerd met behulp van een gestandaardiseerde dataextractie-tabel.

Resultaten: De zoekstrategie heeft 539 artikels opgeleverd, waarvan er 23 werden weerhouden voor kwalitatieve analyse. Over het algemeen worden prevalentie, ernst van en het tijdstip waarop de afwijkingen van de HPA-as zich presenteren in verband gebracht met de totale stralingsdosis en fractionering, leeftijd op het moment van diagnose, leeftijd bij aanvang van radiotherapie en follow-up lengte. De meest voorkomende afwijking van de HPA-as is een groeihormoondeficiëntie(12.5-100%), gevolgd door centrale bijnierinsufficiëntie(0-43%), centrale hypothyroïdie(0-67%), hypogonadotroop hypogonadisme(0-20.4%), pubertas praecox(4.6-26%), hyperprolactinemie(0-57%) en tot slot centrale diabetes insipidus(0-10.5%), wat zelden voorkomt. De incidentiecijfers van zowel centrale hypothyroïdie, hypogonadotroop hypogonadisme als afwijkingen van de gemiddelde lengte van de patiënten liggen significant lager bij patiënten die behandeld werden met protonradiotherapie.

Conclusie: Radiotherapie veroorzaakt een breed spectrum van afwijkingen met betrekking tot de HPA-as bij kinderen met een hersentumor. Voornamelijk de adenohypofysaire hormonen zijn hierbij betrokken, groeihormoon in het bijzonder. Afwijkingen van de hormonen van de neurohypofyse zijn eerder zeldzaam. Recente ontwikkelingen in radiotherapeutische behandelingsmodaliteiten lijken veelbelovend om de radiotherapie-geïnduceerde neveneffecten op de HPA-as te beperken, hoewel verder onderzoek noodzakelijk is.

4. INTRODUCTION

In this article we aim to discuss the radiotherapy-induced effects on the hypothalamic-pituitary-adrenal axis in children diagnosed with a brain tumour.
Incidence rates of brain and other nervous system tumours in children, aged 0-14 years, and adolescents, aged 15-19 years, have been stable over the last few years (approximately 3.5/10000 and 2.3/10000 respectively) with a 5-year survival rate now close to 80%[1]. These rates differ between the various types of brain tumours. An overview of the most common central nervous system tumours in Belgium is provided in figure 1[2]. Astrocytomas are most frequently diagnosed (43%). Note that in the youngest age group ependymomas presented as the most frequent central nervous system tumour.

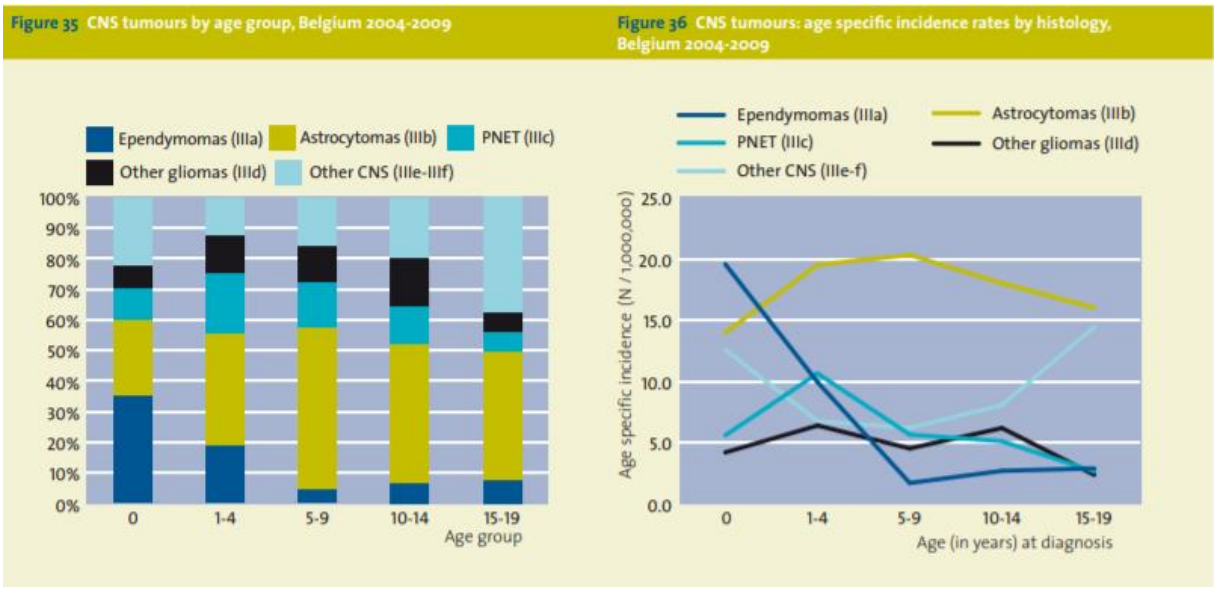

Figure 1: Tumours of the central nervous system in the Belgian pediatric population (2004-2009).
Figure 35 shows distributions of diagnoses sorted by age group. Figure 36 shows age specific incidence sorted by age group at diagnosis[2].

Due to contemporary technical and medical advances in treatment our 5-year survival rate is nowadays higher than ever. However, this withholds the disadvantage of long-term adverse effects of cancer treatment and their impact on functional outcomes and quality of life, including endocrine effects.

In pediatric cancer survivors, up to 50% will experience one or more hormonal disorder(s) throughout their lives[3]. Often, these disorders are related to the management and treatment modalities in children diagnosed with a brain tumour. The management of brain tumour treatment nowadays depends on histological type, patient's age, tumour location and its extent. The treatment typically involves neurosurgery, chemotherapy and/or radiotherapy[4].
Especially the hypothalamic-pituitary-adrenal axis is influenced by radiotherapy and therefore entails major therapy-induced endocrine disorders. The HPA axis consists of

several sub-axes and thus synthesizes a whole range of hormones, cfr. Figure 2, which can all be affected by radiotherapy[5].

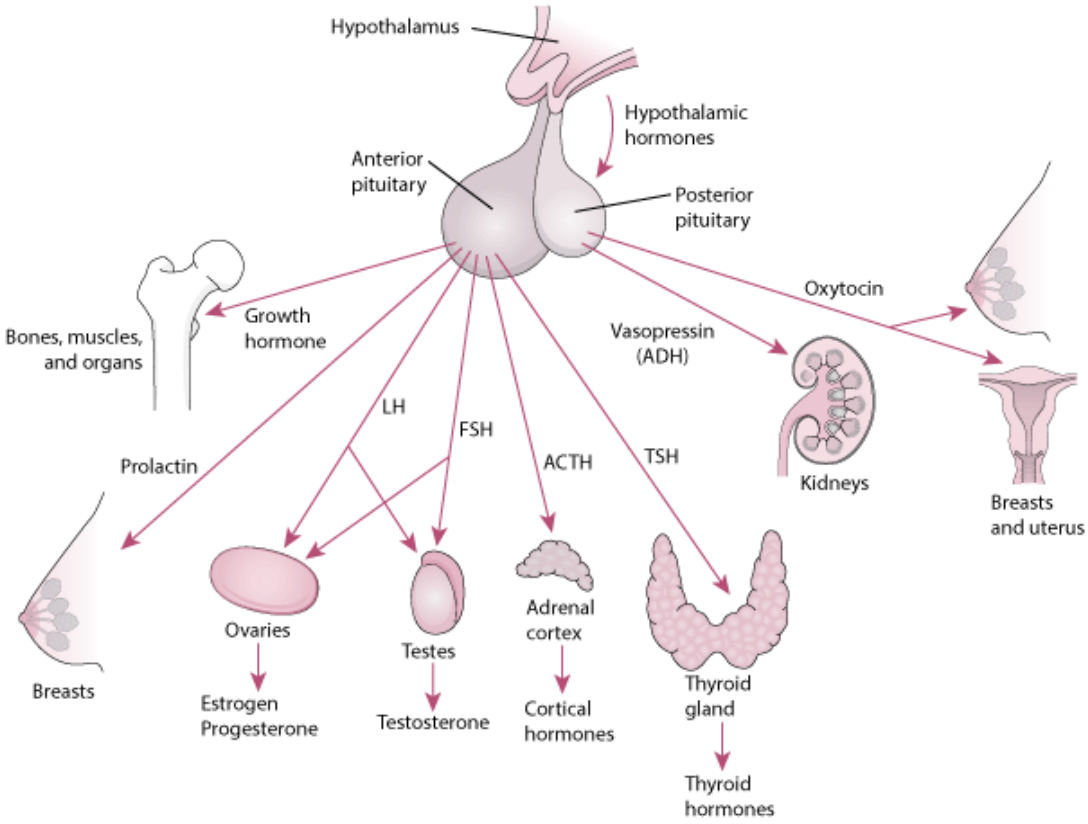

Figure 2. An overview of the Hypothalamic-Pituitary-Adrenal axis and their hormones. Derived from https://www.msdmanuals.com/professional/endocrine-and-metabolic-disorders/principles-of-endocrinology/overview-of-the-endocrine-system[5].

The purpose of this systematic review is to synthesize current evidence of radiotherapy-induced effects on the hypothalamic-pituitary-adrenal axis in children diagnosed with a brain tumour. More specifically, the various types of radiotherapeutic treatment modalities and their dose dependent influences on the HPA axis, the specific brain tumours found in our selected studies, and their follow-up time will be discussed. We will zoom in on the different hormones of the HPA-axis separately to provide an overview on their specific deficiencies. Eventually the methodological limitations of the reviewed articles will be discussed, as well as the future directions they present regarding radiotherapeutic treatment options, minimizing endocrine disorders.

5. METHODS

Search strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[6]. We performed an extensive literature search in June 2019 using the PUBMED/Medline database. To investigate radiotherapy-induced endocrine sequelae in childhood brain tumour patients, our search strategy was based on four major components using the MESH database. (1) ("Infant"[Mesh] OR "Adolescent"[Mesh] OR "Child"[Mesh]), (2) ("Hypothalamo-Hypophyseal System"[Mesh] OR "Adrenal Glands"[Mesh] OR "Pituitary Gland"[Mesh]), (3) ("Brain Neoplasms"[Mesh]), (4) ("Therapeutics"[Mesh]). Three additional search restrictions were applied, including: date of publication (i.e. <10 years), human studies only and full text availability. Detailed search terms are presented in figure 3.

Study selection

First, we reviewed the selected articles by abstract. Second, the full text was analyzed according to our inclusion criteria. Finally, we included additional articles by manual citation tracking through our included articles.

Publications were found suitable for inclusion in this review if they met all of the following criteria: (1) review, meta-analysis or original research article about (2) cranially irradiated (3) pediatric (4) brain tumour survivors, which investigated the effects of radiotherapy on the (5) HPA-axis. Logically, publications were only included when they (6) were published in the English language. Case reports; commentaries; editorials; conference abstracts; in vitro studies or non-human studies; articles not related to brain neoplasms; articles not related to therapy-induced effects; articles not related to pediatrics or articles involving only information about adults; articles related to surgery or surgical techniques; articles related to specific medical techniques or articles not related to the defined outcomes of interest were excluded (figure 3).

Data extraction

Data were extracted from the 23 included publications using a standardized data extraction table (supplementary table 1 and 2).

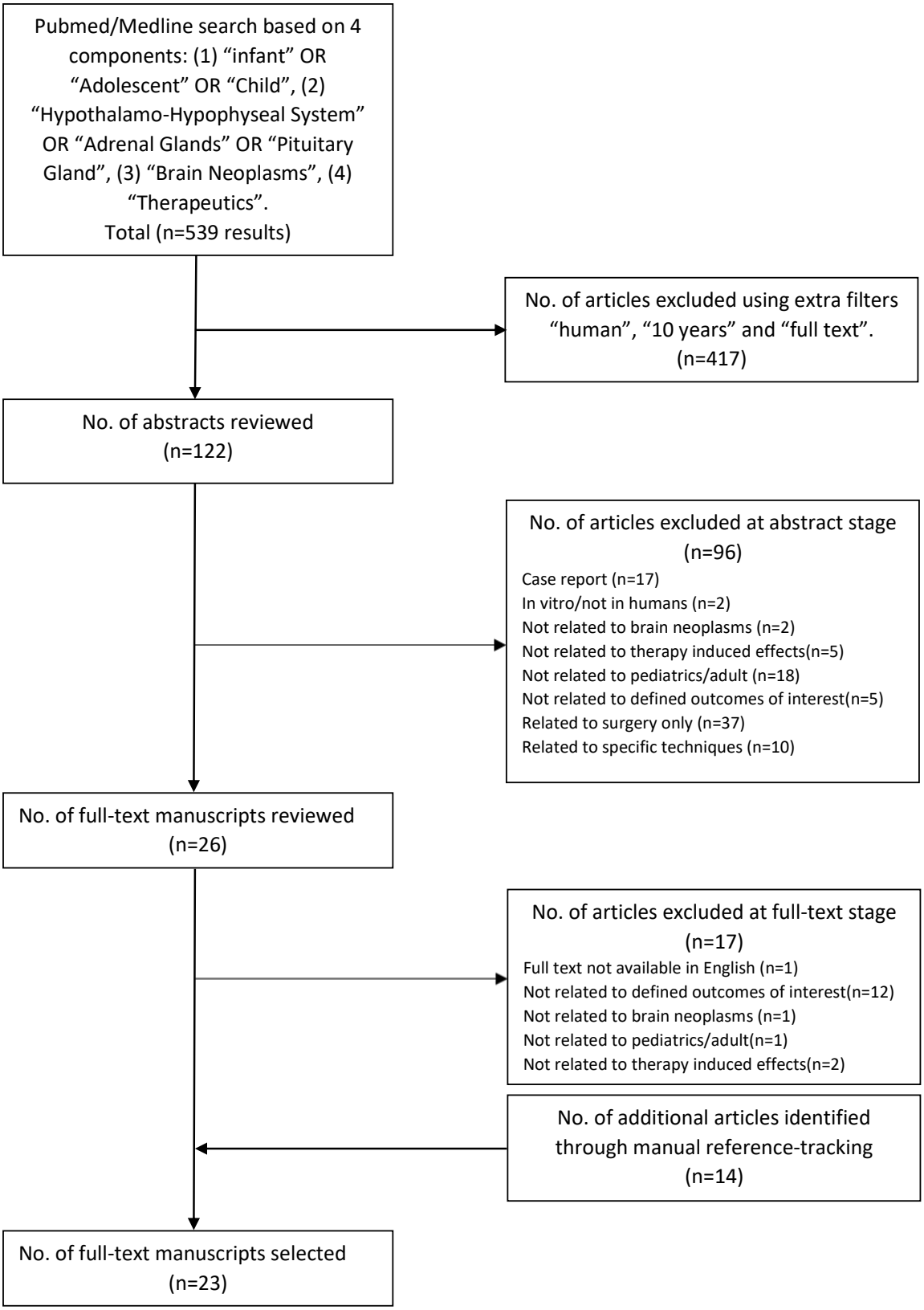

Figure 3. Flow diagram showing the study selection process and criteria of the included studies.

6. RESULTS

6.1 Study characteristics

After screening 539 articles, 23 studies were included. Supplementary table 1 and 2 represent the characteristics of the selected studies. Supplementary table 1 presents the original research articles, which involve a total of 4695 participants. Supplementary table 2 presents 6 review articles.

In ten articles a retrospective cohort study design was used[7-16], of which one also conducted a literature review[14]. Two articles applied a prospective cohort design[17,18]. Four articles implemented a longitudinal study design[19-22]. One article used a population-based cohort study and this was also the only study in which a healthy control group was included[23].
The most common types of pediatric brain tumours examined in our selected articles were glioma[7-9,12-16,21-23], medulloblastoma[7,9,11,13-18,21,23], ependymoma[7,9,11,14-16,21], astrocytoma[7,9,11,16,21,23], germ cell tumours[7,13,15,16,21,23] and neuro-ectodermal tumours[7,13-15,18,21,23]. Pituitary adenomas were only mentioned in one article[10]. One article did not specify the type of pediatric brain cancer[19] and one article made a selection based on the ICD-10 criteria[20]. A more detailed description of the evaluated types of pediatric brain tumours is given in supplementary table 1.
The selected articles describe different types of cranial radiation therapy used. In eleven articles the treatment modality was conventional photon radiotherapy[9,11-16,19,21-23], of which two articles used the biologically effective dose to describe the radiation dose on the tissues[11,23]. One article evaluated proton radiation therapy[8], another proton versus photon radiation therapy[17] and one article evaluated proton versus proton plus conventional photon radiotherapy[7]. One article assessed conformal radiation therapy[18], another radiotherapy via Gamma Knife surgery[10] and in one article radiotherapy was not further specified[20]. Eight articles described additional spinal radiation therapy next to cranial radiation therapy[9,12-18], and in six articles not all the included patients were treated with radiation therapy[13-16,20,22].
Fifteen articles analyzed the radiotherapy-induced effects on growth hormone (GH) or height SDS[7-18,20-22]. Thirteen studies analyzed ACTH and cortisol levels[7,8,10-18,22,23]. Thirteen articles focused on TSH and the thyroid gland[7,8,10-18,20,22], as there were twelve articles which analyzed gonadotropins and LH, FSH function[7,8,10-14,16,17,20,22]. In only four studies the influence of radiotherapy on prolactin levels was documented[8,11,14,22], and in five articles ADH and diabetes insipidus was evaluated[8,13,16,20,22,13,16]. In the following chapters we will give a more detailed description of the radiotherapy-induced effects on the different axes separately.

The articles presented in supplementary table 2 consisted of 4 review articles[24,25,26,27], a review article which included a dose guide[28] and a case series including a literature review[29].

6.2 Hypothalamic-Pituitary-Adrenal axis (HPA axis).

We will discuss the results based on the different sub-axes of the Hypothalamic-Pituitary-Adrenal axis shown in figure 2.

In general, according to Scoccianti et al. (2015), HPA axis dysfunction is present in up to 80% of the patients treated with radiotherapy on the pituitary gland[28]. Prevalence, severity of symptoms and time to onset of dysfunction are related to the total radiation dose, fractioning of the radiation dose, age at time of radiotherapy and the follow-up duration. The selected research articles support these findings. They all report significant effects of radiotherapy on the HPA axis and most of them found a dose dependent correlation, i.e. a higher radiation dose led to more HPA axis disorders[8,10-19,21-23]. Specific risk factors were younger age at diagnosis[16,18,20], younger age at treatment[13,15], fractioning of the radiation dose[11,23], tumor location[11-13,20,22], advanced follow up time[11-16], previous history of radiotherapy[20]. Radiosensitivity, also a risk factor, depends on the different cell populations of the sub-axes and, more specific, the GH axis is the most radiosensitive followed by gonadotropins (i.e. LH and FSH), ACTH and TSH sub-axes[30,31].

Higham et al. (2016) presented the same findings as Scoccianti et al. (2015) for conventional, external photon beam radiotherapy[26]. They also evaluated newer methods of radiotherapy to pituitary tumours such as Gamma Knife surgery (GKS) and Proton Beam Radiotherapy (PBRT), which should result in less damage to the surrounding tissues and therefore reduces HPA axis dysfunction. The findings indeed support the hypothesis of a lower prevalence of hypopituitarism, but further investigation is necessary[32]. Section 7.3 will zoom in further on these future directions.

For a more detailed view on the different aspects of the included articles regarding outcome variables and prevalence data, I refer to supplementary table 1.

6.2.1 Growth Hormone(GH)

Fifteen articles were identified which examined growth hormone deficiency after cranial radiation therapy in childhood brain tumour survivors[7-18,20-22].

These articles based their findings on clinical examination, i.e. height, and/or routine laboratory assessment. Laboratory assessment consisted of measuring growth hormone levels, IGF-1 levels and/or peak stimulated growth hormone values, using ITT, arginine tolerance test and/or l-dopa test. GH deficiency was diagnosed in a wide range of 12.5%-100%.

The growth hormone (GH) revealed to be the first affected hormone, and thus the most radiosensitive in seven articles[11,13,15,16,20,22,23]. It is also the most frequent complication after radiotherapy according to three articles[11,15,20].

Surprisingly, Laughton et al. (2008) found no statistical significance between the radiotherapy dose to the hypothalamus and the incidence of GH deficiency[18]. This could be explained by their high mean radiotherapy dosage, which is higher than the reported threshold of 27 Gy, where almost all patients develop a GH deficiency. This threshold was also supported by Heo et al. (2019) and Aloi et al. (2017), where almost all patients who received a radiation dose of 30 Gy, 40 Gy or higher, developed a growth hormone deficiency[12,20].

A difference in cranial versus craniospinal irradiation was reported by Ramanauskiene et al. (2014)[15]. A higher prevalence of GH deficiency was reported in the craniospinal irradiated group. They also found a male predominance, which was reported by Eaton et al. (2016) as well[17]. Eaton et al. (2016) furthermore presented age at diagnosis as a significant risk factor, i.e. younger age at diagnosis entails a higher incidence of growth hormone deficiency, which is also supported by Shalitin et al. (2011)[16]. The latter reported prepubertal, younger age at time of irradiation and histologic tumour type, i.e. medulloblastoma and optic glioma, as significant risk factors as well. Aloit et al. (2017) reported the influence of tumour location, i.e. closer to the HPA axis, as significant according to development of a GH deficiency[12].

Finally, the research by Clement et al. (2014)[14] is worth mentioning, as they conducted a literature review of 22 studies[11,18,33-52], of which 2 studies were already included in our literature search[11,18]. They reported a growth hormone deficiency of 13-100% in the first five years after brain tumour diagnosis/treatment[11,18,37-41,47,48,51].

Four articles evaluated GH deficiency based on mean adult final height, percentiles of adult final height (AFH) and their associated outcome of short stature[9,15,16,21]. Overall, a significant lower mean adult final height was found in the irradiated population and short stature presented in a range of 17.5%-40%.

Beckers et al. (2010) compared the influence of GH substitution on adult final height in patients treated with cranial radiotherapy (CRT) or craniospinal radiotherapy (CSRT)[9]. They both presented with a lower adult final height, but GH substitution resulted in a significantly lower AFH in the craniospinal irradiated group. Craniospinal irradiation therapy, young age at end of treatment and short stature were risk factors for a low adult final height.

Gurney et al. (2003), Ramanauskiene et al. (2014) and Shalitin et al. (2011) also reported short stature[15,16,21]. Cranial irradiation[15,16], craniospinal irradiation[15,16], radiotherapy dose to HPA axis[21], male sex[21], and young age at diagnosis[16,21] were significant risk factors.

Regarding specific findings about the influence of proton radiation therapy, Eaton et al. (2016) described that proton radiation therapy resulted in higher height standard deviation scores than photon radiation therapy[17]. With regards to GH deficiency there were no significant differences (proton 52.5% vs. photon 56.76%). Greenberger et al. (2014) reported a long-term 60% chance of growth hormone deficiency after proton radiotherapy(mean dose >40Gy) in childhood low-grade gliomas[8]. Finally, Viswanathan et al. (2011) compared proton beam radiation therapy (PBRT) with conventional plus proton beam radiation therapy (CPBRT)[7]. No significant differences were reported in prevalence of GH deficiency, nor in any other sub-axes. Overall, pituitary hormone deficiencies were earlier detected in the CPBRT group, but they also received a higher radiation dose. Therefore, it is not possible to attribute these findings to the radiotherapy type only.

6.2.2 Adrenocorticotropic Hormone(ACTH) and Cortisol

Thirteen of the included articles evaluated the radiotherapy-induced effects on ACTH and cortisol[7,8,10-18,22,23].

In the articles central adrenal insufficiency was measured by blood samples evaluating basal morning cortisol levels and/or cortisol levels after specific stimulation tests, i.e. ACTH test/Synacthen test and/or insulin tolerance test (ITT). Note that our studies used different cut-off values for cortisol measurement. Central adrenal insufficiency was reported in a range of 0%-43%. Clement et al.'s (2014) literature review supports these findings[11,14,18,33-36,38-40].

Schmiegelow et al. (2003) showed a relatively high prevalence of central adrenal insufficiency, but identified a discrepancy in response to an ACTH and an ITT test[23]. 33 of 73 patients had undergone both an ACTH and an ITT test, from which 10 of the 33 patients reported no deficiency after an ACTH test, but did after the ITT test. This questioned the relevance of the ACTH test as a first-line screening test.

Shalitin et al. (2011) showed a predominating trend of central adrenal insufficiency in patients who were treated with CRT versus CSRT and had a suprasellar tumour location, but these differences were not statistically significant[16].

Clement et al. (2016) presented a lower prevalence of central adrenal insufficiency compared to GH, gonadotropin and TSH deficiency[13].

According to Spoudeas et al. (2003) radiotherapy induced central adrenal insufficiency was not significant, but rather of a multifactorial etiology[11].

Concerning proton radiotherapy, Greenberger et al. (2014) reported a 22% long-term chance of central adrenal insufficiency, 10 year post-treatment, in childhood low-grade gliomas who had received proton radiotherapy with a median radiation dose of more than 40 Gy[8]. Eaton et al. (2015) evaluated central adrenal insufficiency in proton versus photon radiotherapy, but found no significant difference (5% vs. 8.11% respectively)[17].

6.2.3 Thyroid Stimulating Hormone(TSH)

The search strategy rendered thirteen articles which evaluated the radiotherapy-induced effects on TSH and the thyroid gland[7,8,10-18,20,22]. In all these articles TSH activity was measured by routine blood sample analysis of TSH levels and/or free thyroxine. Outcome variables were central hypothyroidism, primary hypothyroidism and radiation-induced tumours. In general, this sub-axes presented to be the least radiosensitive according to Aloi et al. (2017) and Shalitin et al.(2011)[12,16].

Central hypothyroidism was diagnosed when blood samples showed a low free thyroxine value with a low to normal level of TSH, and was reported in a range of 0%-67% in the selected articles[7,8,10-18,20,22]. Clement et al.'s (2014) literature review supported these findings after a 5-year follow-up[11,14,18,33-35,38-41,47,49,50].

More specific, two articles reported that central hypothyroidism was dose-dependent, i.e. a higher RT dose was associated with a higher risk of developing a deficiency[12,18].

According to two articles, patients with a medulloblastoma seemed to be more prone to central hypothyroidism[13,20]. Also, additional chemotherapeutic treatment and craniospinal

irradiation were risk factors[14,17]. One article reported radiotherapy to be a risk factor, but not independently though[22].

With regards to proton radiation therapy, Greenberger et al. (2014) reported a long-term 45% chance on central hypothyroidism after proton radiotherapy(median radiation >40 Gy)[8]. Eaton et al. (2015) found a statistically significant difference in proton (22.5%) versus photon (64.9%) radiotherapy in the development of central hypothyroidism[17]. They also reported a near complete avoidance of the thyroid and gonads compared to photon therapy.

Primary hypothyroidism was diagnosed in four articles[13,15,16,20]. They were significantly associated with craniospinal irradiation, possibly induced by scattered radiation. The total dose on thyroid gland[15], duration of follow up[13,15,20], cranial irradiation[15,16] itself and younger age at diagnosis[13] were identified as significant risk factors.

Other relevant findings were a risk of radiation-induced thyroid tumours by Heo et al. (2019) and Shalitin et al. (2011), especially after craniospinal irradiation and after an extensive follow-up time[16,20]. Shalitin et al. (2011) also reported a higher prevalence of goiter and thyroid noduli in patients who received craniospinal radiotherapy[16].

6.2.4 Gonadotropins (Luteinizing Hormone(LH) and Follicle-Stimulating Hormone(FSH))

Twelve articles were identified which examined gonadotropins[7,8,10-14,16,17,20,22]. Relevant outcomes were hypogonadotropic hypogonadism and precocious puberty. Also, in some articles primary gonadal deficiency was reported[11,13,14,17]. Finally, 2 articles based their findings on fertility, pregnancy status and/or permanent amenorrhea[19,27].

Eight articles described hypogonadotropic hypogonadism, which was diagnosed if patients showed absence of puberty with low serum gonadotropin levels[7,10,12-14,16,17,22]. They all found significant numbers of hypogonadotropic hypogonadism in their study populations, range 0%-20.4%.

Feigl et al. (2010) surprisingly reported the gonadal axis to be the most radiosensitive after GKS[10]. Shalitin et al. (2011) reported a significant lower risk at developing a gonadotropin deficiency in patients diagnosed with a medulloblastoma[16]. Clement et al. (2016) reported older age at primary cancer diagnosis to be a significant risk factor[13].

Regarding proton radiation therapy, Eaton et al (2015) found a statistically significant difference between proton (3%) and photon (19%) radiotherapy[17] as to developing hypogonadotropic hypogonadism. Greenberger et al. (2014) measured testosterone levels to identify gonadotropin deficiency and reported a long-term 18% chance of gonadotropin deficiency in low-grade gliomas with a median radiation dose of more than 40 Gy[8]. Viswanathan et al. (2011) reported no statistically significant difference between the PBRT and CPBRT group[7].

Four articles reported precocious puberty in a range of 4.6%-26%[13,16,20,22]. Shalitin et al. (2011) reported a higher prevalence in patients with a younger onset of puberty and younger age[16]. Gan et al. (2015) and Clement et al. (2016) reported that radiotherapy was not an independent risk factor for precocious puberty[13,22]. Also, comparing proton with

photon radiotherapy, Eaton et al (2015) found no significant differences as to precocious puberty[17].

Primary gonadal deficiency is especially accounted for after associated spinal irradiation[13,14,17].
Spoudeas et al. (2003) also identified primary gonadal deficiency in 2 patients, but these had received adjuvant chemotherapy, which was known for its gonadal toxicity[11]. This chemotherapy-induced gonadal toxicity is corroborated by Clement et al. (2014; 2016)[13,14] As a result, the radiotherapy-related effects were non-significant.

Koustenis et al. (2013) evaluated gonadotropin deficiency based on pregnancies, infertility and permanent amenorrhea[19]. They divided their patients into subgroups according to the radiotherapy dose received. Survivors receiving ≥30 Gy presented significantly less pregnancies, more infertility and more permanent amenorrhea than in the other subgroups.

One review article focused on fertility in childhood cancer survivors (Vern-Gross et al. (2015))[27]. They reported that infertility is influenced by cranial radiation in a negative way, but that it is often overlooked and underreported. Further prospective trials are needed to evaluate the quality of life outcomes and to identify potential new biomarkers for infertility and gonadotropin disorders.

6.2.5 Prolactin

Four articles examined the effect of radiotherapy on PRL levels[8,11,14,22], measured by routine laboratory assessment. Hyperprolactinemia was reported in a range of 0%-57%.

Spoudeas et al. (2003) and Gan et al (2015) reported no significant cases of hyperprolactinemia after a mean follow-up time of 11 and 8.3 years respectively[11,22].

Complementary to these findings, Clement et al. (2014) retrospectively evaluated PRL levels in 19 childhood brain tumour survivors, treated with surgery, radiotherapy, chemotherapy or a combination[14]. None of the patients had developed any form of hyperprolactinemia after a median follow-up of 2.4 years. They also conducted a literature review in childhood brain tumour survivors in which they found five relevant articles that described hyperprolactinemia (range 0-57%)[33-36].

Regarding proton radiotherapy, Greenberger et al. (2014) reported a long-term 15% chance of elevated PRL levels in childhood low-grade gliomas treated with proton radiotherapy with a median radiation dose of more than 40 Gy[8].

6.2.6 Antidiuretic Hormone

Radiation-induced damage to the hypothalamic-pituitary axis presents usually with anterior pituitary hormone deficiencies, but can, unusually, also present as a posterior pituitary hormone deficiency[53]. Therefore, ADH deficiency can occur leading to central diabetes insipidus.
Five articles examined the risk of treatment-related central diabetes insipidus[8,13,16,20,22], which was measured through routine laboratory assessment of ADH levels and/or a water deprivation test. Central diabetes insipidus prevalence ranges between 0%-10.5%.

Clement et al. (2016) reported an ADH deficiency in 2.6% of his included patients[13]. This was solely diagnosed in patients with a low-grade glioma or germ-cell tumour and only at diagnosis or after neurosurgery. No specific link between ADH deficiency and cranial radiotherapy was reported in this article. According to Gleeson et al.(2004) ADH deficiency has rarely been reported after cranial radiotherapy[54].

In a retrospective study, Shalitin et al. (2011) found a higher prevalence in patients with optic glioma and in patients who received cranial radiation, albeit non-significant[16].

Regarding proton radiotherapy, Greenberger et al. (2014) reported a long-term 10% chance at central diabetes insipidus in childhood low-grade gliomas treated with proton radiotherapy with a median radiation dose of more than 40 Gy[8].

6.2.7 Oxytocin

There was no evidence found regarding oxytocin abnormalities in the selected articles.

7. DISCUSSION

7.1 Summarization of radiotherapy induced effects and their risk factors

The purpose of this systematic review was to summarize literature findings on the effects of radiotherapy on the HPA axis in children with a brain tumour. The results of our selected studies showed that radiation therapy plays an important role in endocrine disorders of the HPA axis.

Figure 4 shows the sub-axes that were affected by radiotherapy. In general, prevalence, severity of symptoms and time to onset of dysfunction are related to the total radiation dose, fractioning of the radiation dose, age at time of diagnosis, age at start of radiotherapy and to follow-up duration. The results reveal that radiotherapeutic dose-dependent effects seem to be the greatest independent risk factor for developing an HPA axis disorder. As a result, the effects of conventional photon radiotherapy and newer treatment modalities, e.g. proton beam radiation therapy, were compared in order to evaluate significant differences and potentially reduce HPA axis disorders. We found a statistically significant lower incidence of central hypothyroidism, hypogonadotropic hypogonadism, as well as a significantly greater mean height at last follow-up among patients treated with proton beam radiation therapy. Limitations to these findings were a relative narrow spectrum of brain tumor types and a rather limited amount of articles. Further investigation is necessary to provide a more holistic view on the advantages of proton beam radiation therapy.

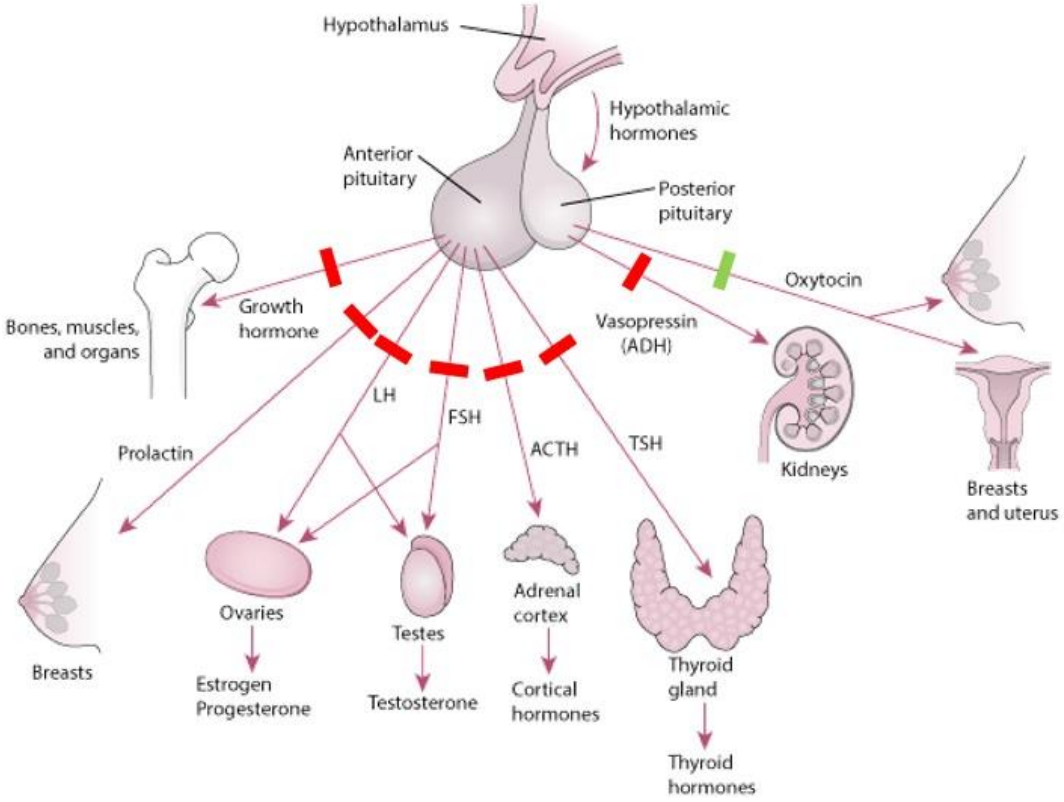

Figure 4. An overview of the Hypothalamic-Pituitary-Adrenal axis and the radiotherapy affected hormones. Red bars withhold an effected axis. Green bar withholds a not effected axis.

Overall, anterior pituitary hormones were more affected then posterior pituitary hormones, which is consistent with the findings of Jyotsna et al. (2001)[53].

GH deficiency revealed to be the most common deficiency, but the selected articles presented a a great difference regarding prevalence. Overall, it is the earliest detected and thus earliest affected axis, which confirms it to be the most radiosensitive hormone. In addition, short stature was also very common, but these findings should be interpreted with great care. Treatment with spinal radiation therapy could bias our findings, based its local effect on the vertebrae.

ACTH and cortisol disorders (central adrenal insufficiency), TSH disorders (central, hypothyroidism, primary hypothyroidism, thyroid tumours), gonadotropin disorders (hypogonadotropic hypogonadism, precocious puberty, primary gonadal deficiency and gonadotropin deficiency based on pregnancy, infertility and permanent amenorrhea), and especially prolactin disorders (hyperprolactinemia) were less frequently present after radiotherapy. Note that craniospinal irradiation has a significant direct effect on the thyroid gland and gonads. Therefore results on thyroid tumors and primary gonadal deficiency should be interpreted with care. Also, TSH disorders seemed to be the least radiosensitive.

Posterior pituitary hormone deficiencies, i.e. ADH (central diabetes insipidus), presented to be less frequent than anterior pituitary hormone deficiencies, but results were rather limited, likely due to their relatively low prevalence rate. There was no evidence found regarding oxytocin.

7.2 Limitations to the study

The included studies were very heterogenous and represented a large cohort. Furthermore, a brought spectrum of pediatric brain cancer types, a wide variety in radiation therapy modalities and a great variety of hormonal outcomes were described, which account for several strong points of the present literature review. Nonetheless, several limitations were identified.

A first shortcoming concerns the study design of the selected articles. Most of the articles were retrospective cohort studies, and only two articles resorted to a prospective cohort design. Furthermore, only one article included a healthy control group. It would be useful for future research to carry out more prospective studies with inclusion of healthy controls. Also, double-blind studies could give a more broadened view on the different radiotherapeutic treatment modalities, but is, considering the delicate and ethical subject, a rather sensitive matter.

Secondly, the articles described a great variety of study sample sizes, time of follow-up, histological tumor types and implemented tests (cfr. supplementary table 1). This could lead to a bias in the results and to a significant difference in outcome percentages and prevalence rates of endocrine disorders between the studies. A longer follow-up period gives us a better overview of late endocrine effects and a more thorough evaluation regarding very late occurring disorders.

Another important consideration regarding our study population is the involvement of radiotherapeutic treatment. Not all studies evaluated the effects of radiotherapy only, but also included surgical and/or chemotherapeutical treatment. All of these treatment options can have an influence on the HPA axis. Therefore some findings should be interpreted with great care.

7.3 Future directions

Radiotherapeutic treatment is constantly developing in order to improve disease control while limiting radiotherapy-induced toxicity. Regarding future technologies and optimizing radiation therapy Ludmir et al (2018) reported several modalities that could reduce radiotherapeutic effects on the healthy tissue, including the HPA axis[55].

Firstly, before radiotherapy could be administered, a CT simulation is implemented to optimize the patient's position for treatment. CT simulation, however, has a relatively poor soft-tissue contrast, thus nowadays MRI is preferred, which shows a high soft-tissue contrast. Co-registration of MRI and CT has resulted in better contouring of targeted volumes as well as increased protection of soft-tissue areas[56,57]. Furthermore, dedicated MRI simulators are increasingly used in several hospitals. These simulators provide imaging sequences in the radiotherapeutic treatment position, which results in an additional positive effect on protecting the soft tissues[58].

Advances in photon radiotherapy itself were also described by Ludmit et al. (2018). 2D and 3D conventional photon radiotherapy are now widely associated with intensity-modulated radiotherapy (IMRT). IMRT uses multileaf collimators, which subdivide each radiotherapy beam into several smaller beamlets. This technique leads to a higher dose on the tumour region and reduces the radiotherapeutic dose on the healthy tissues. In the treatment of brain tumours, IMRT has been shown to improve target conformity as well as

healthy tissue sparing when compared to standard conventional photon radiation therapy[59-61]. In addition to IMRT, arc-based therapies are increasingly used. An example of these arc-based therapies is volumetric modulated arc therapy (VMAT). VMAT is based on coplanar intensity-modulated arcs in which the linear accelerator gantry rotates around the patient and is more dynamic in its radiation delivery. Outcome tends to be better than IMRT, especially in accordance to target volume dose and healthy tissue sparing, but the biggest advantage is speed of treatment delivery[62-65]. Where IMRT takes around 30 minutes, VMAT takes only 10 to 15 minutes, which is particularly advantageous in pediatric patients.

Stereotactic radiotherapy represents another option, which is a photon-based technique delivering large doses in a highly precise way to a rather small and spherical target, often delivered as a single fraction or over just a few fractions. An example of this technique is Gamma Knife surgery, evaluated by Feigl et al. (2010), which reported a trend of lower pituitary insufficiencies after GKS[10]. To date, it is mostly used in the treatment of brain metastases in pediatric patients, as a stand-alone treatment modality in low-grade gliomas[66-73]. An advantage is the rather small or no fractioning of the therapeutic dose, which reduces the burden of prolonged treatment duration. Its highly precise technique minimizes the effects on the healthy tissue.

Finally, specific new therapies are being increasingly implemented in clinical practice. Proton beam therapy and other particle therapies, such as carbon ions, are treatment modalities showing major advances. Photon radiotherapy is delivered from its entrance into the body to a maximum radiation dose, and then continues to deliver a radiation dose until it exits the body. In contrast, proton beams decrease velocity as they pass through the body and deposit more radiation when decreasing velocity until they reach a stopping depth. This is the point where they deposit the highest radiation dose, which results in a minimal exit dose. This minimal exit dose presents a major advantage and therefore minimizes normal tissue radiation exposure. Multiple dosimetric studies have confirmed these benefits of proton beam radiotherapy[74-79]. Also, the effect on tumours seemed to be comparable to that of photon-based radiotherapy, while clinically meaningful reductions in toxicity were reported[17,80-89].

All of these techniques attempt to optimize the radiotherapeutic dose on the tumorous tissue and minimize treatment-related toxicity. Regarding HPA axis toxicity, these techniques can have an important role in reducing endocrine disorders. Yet further investigation of the influence of these specific treatment options is necessary to evaluate their long-term effects.

8. CONCLUSION

A broad range of hypothalamic-pituitary-adrenal axis deficiencies were analyzed and described in this systematic review. In childhood brain tumor survivors treated with radiotherapy, anterior pituitary hormones revealed to be frequently affected, growth hormone in specific. Posterior pituitary hormone deficiencies were rather uncommon.
Additional findings on newer radiotherapeutic treatment modalities, especially proton beam radiation therapy showed to be hopeful, but long-term data remain rather limited. Future directions include better treatment planning based on MRI, advances in conventional

photon radiotherapy, i.e. IMRT and VMAT, stereotactic radiotherapy, proton beam radiation therapy and other particle radiotherapies. These modalities can possibly minimize the radiation dose to the surrounding normal, healthy tissue. Nevertheless, further long-term investigation regarding these modalities is necessary to evaluate their radiotherapy-induced effects on the hypothalamic-pituitary-adrenal axis and quality of life.

9. CONFLICTS OF INTEREST

None.

10. FUNDING

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13. Ethical agreement

KU LEUVEN

SCONE

Geachte professor,
Beste student,

De verstrekte informatie toont aan dat het onderzoek in het kader van de masterproef een zuivere literatuurstudie betreft en dat er op geen enkele wijze gebruik wordt gemaakt van proefdieren, proefpersonen of menselijk lichaamsmateriaal.

Dit type onderzoek vereist geen goedkeuring van een gemachtigde commissie voor medische ethiek.

Onder voorbehoud van de volledigheid en correctheid van de door u verstrekte gegevens, krijgt u hierbij het akkoord om het onderzoek in het kader van de masterproef te starten. Deze mail dient als bewijs van goedkeuring mocht u uw onderzoek wensen te publiceren.

Wij willen u erop attent maken dat u zelf verantwoordelijk blijft voor uw onderzoek. Bovendien doet elke wijziging aan de door u verstrekte gegevens omtrent de onderzoeksopzet deze goedkeuring vervallen. U dient in dat geval een amendement te maken aan uw huidig dossier.

Veel succes!

Heeft u vragen? Kijk dan zeker eens bij de uitgebreide documentatie op SCONE.
Do you have questions? Check out the extensive documentation on SCONE.