The Late Effects of Cranial Irradiation in Childhood on the Hypothalamic-Pituitary Axis: A Radiotherapist’s Perspective
**Full Title:** The Late Effects of Cranial Irradiation in Childhood on the Hypothalamic-Pituitary Axis: A Radiotherapist’s Perspective

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**Short Title:** Late Effects of Brain Radiotherapy in Children

**Key Words:**
- Neuroendocrine disruption
- Hypothalamic-pituitary axis
- Radiotherapy
- Hormone deficiency

**Word Count:** 5156
Abstract

Brain tumours make up nearly one third of paediatric malignancies. Over time, advancements in oncological treatments like radiotherapy have helped reduce normal-tissue toxicity when treating cancers in the brain. However, clinicians are still faced with a trade-off between treatment efficacy and potential side effects. The aim of this review is to address the late effects of cranial irradiation on the neuroendocrine system, and to identify factors that make patients more vulnerable to radiation-induced endocrine sequelae. Radiation damage to the hypothalamic-pituitary axis, which orchestrates hormone release, can lead to endocrinopathy; up to 48.8% of children who have undergone cranial irradiation develop a hormone deficiency. This may lead to further health complications that can appear up to decades after the last treatment, lowering the patients’ quality of life and increasing long-term costs as lifelong hormone replacement therapy may be required. Growth hormone deficiency is the most common sequelae, followed by either thyroid or gonadotrophic hormone deficiency. Adrenocorticotrophic hormone deficiency tends to be the least common. Identified factors that increase the risk of late endocrine deficiency include total radiation dose, age at treatment, and time since last treatment. However, as there are various other factors that may potentiate the damage, a universal solution proven to be most effective in sparing the endocrine tissues is yet to be identified. Until then, accounting for the identified risk factors during treatment planning may in some cases help reduce the development of endocrine sequelae in childhood cancer survivors.

Introduction

Around one third of paediatric malignancies occur within the cranium. (1). As summarised in Table 1, gliomas and embryonal tumours are the most common tumours in children, each with a prevalence of up to 43% and 20% respectively. Tumours such as ependymomas, craniopharyngiomas, germ cell tumors, and choroid plexus tumours are much less common, and each have a prevalence below 10% (2). Although oncological therapies have evolved over time, a balance between treatment efficacy and detrimental side effects, such as secondary neoplasms and endocrine deficiencies, is still needed. As the survival rate has also increased, patients are now living long enough to see these late effects. Common oncological treatments include chemotherapy, radiation therapy (RT), and surgical resection of a tumour. These treatments are often combined to minimise the risk of tumour recurrence. In this
review, the focus is on external beam RT which involves the use of high energy radiation to create DNA breaks in the tumour cells with the aim of reducing proliferation and inducing cell death (3). An advantage of RT is that it can be utilised in many ways; as curative treatment to shrink and eliminate a tumour, to prevent remaining tumour cells from proliferating following surgical resection, and as a palliative treatment to reduce discomfort and increase quality of life in terminally ill patients (4). RT may also be used as prophylactic treatment to prevent spread of cancers such as in small cell lung carcinoma (5). However, cranial irradiation has previously been identified as a risk factor for endocrinopathy. Radiation damage to the hypothalamus and pituitary gland, which orchestrate hormone release from within the brain, can lead to hormone deficiency. This can lead to further unfavourable health problems such as short stature and low bone mineral density (6). Sparing the endocrine system during RT will not only reduce the risk of endocrinopathy and improve the long-term quality of life for the patients, but also benefit the healthcare system financially by reducing the overall treatment costs, as life-long hormone replacement therapy may be avoided. This review aims to address the late effects of cranial RT on the endocrine system, and to identify factors that make patients more vulnerable following the treatment. Ascertaining what increases the risk of post-RT endocrinopathy is the first step in improving treatment methods in order to spare the intracranial endocrine system and improve the well-being of childhood cancer survivors.

**Radiation Therapy: What Is It and How Does It Work?**

External beam RT typically utilises photons generated by directing electrons accelerated to very high energies using a linear accelerator to a target. These photons are then collimated to the shape of the tumour and delivered to the patient to treat the tumour. RT works by damaging tumour cell DNA; it induces various types of lacerations such as single and double strand breaks in the sugar phosphate backbone, with the latter often leading to cell death of the tumour cells, as visualised in Figure 1 (3). Standard photon beam RT treatments deliver 1.8-2.0 Gray (Gy) fractions of radiation dose five days a week for 4-6 weeks (3). The most common types of RT used for paediatric brain tumours are 3D conformal RT (3DCRT) and intensity-modulated RT (IMRT); their differences lie in the ways they conform dose around the tumour volume (7). 3DCRT involves the use of CT scans and manual optimisation of the beam parameters to create an appropriately shaped dose distribution. IMRT, however, uses a computer algorithm in addition to a CT scan, to automatically find the most suitable
radiation plan that matches the given planning parameters. Proton beam RT can also be used; the main benefit of this type of RT is that it reduces exposure of healthy tissue to radiation distal to the tumour due to the absence of an exit dose (7). Advances in modern technology have allowed for more accurate tumour localisation and reduced margins through the use of image guidance. This has meant that the volume of brain exposed to the high therapeutic doses of radiation can be reduced, allowing non-target tissues to be spared more effectively (7). However, like most cancer treatments, RT comes with side effects. These can either be acute effects which occur during and shortly after treatment, or long-term effects that present themselves months to years after treatment. Common, transient, acute side effects include fatigue, hair loss, nausea, and worsening of neurological symptoms caused by the tumour due to swelling in the brain (8). Long-term effects include changes in brain function such as confusion and poor memory, radiation necrosis, and late stochastic effects such as the manifestation of another tumour due to the carcinogenic effects of radiation. Damage to important brain regions, such as the hypothalamus and pituitary gland can lead to detrimental secondary effects such as hormone deficiency, which can further deteriorate the patient’s overall health (8).

The Hypothalamic-Pituitary Axis

Within the brain, the hypothalamus and pituitary gland make up the hypothalamic-pituitary (HP) axis, which is responsible for hormone regulation and release (Figure 2). The hypothalamus responds to various types of stimuli, such as stress, and is the first step in the generation of an endocrine response. It secretes specific releasing hormones via the median eminence which travel through the hypothalamo-hypophyseal portal circulation to the anterior pituitary gland, where they bind to specific cell surface receptors (9). This activates intracellular signalling cascades within the pituitary cells, leading to increased production and secretion of the specific hormone into the periphery, where it will either bind to another gland to stimulate production of the final hormone, or exert direct physiological effects (9). Due to the widespread actions of hormones in the body, endocrine disorders such as hypopituitarism (abnormally low pituitary hormone secretion) caused by cranial irradiation can have a plethora of detrimental effects, some of which are outlined below in Figure 2. Notably, however, these consequences can often be prevented using hormone replacement therapy, given that treatment commences before permanent effects manifest, which may require prompt diagnosis of deficiency.
Relationship Between Radiation Dose and Endocrine Deficiency

The total RT dose, and the age at which RT was received are key factors in the risk of developing endocrine deficiency. A recent study by Xu et al. utilised rat models to investigate the effect of cranial irradiation on the endocrine system; 40 female Wistar rats were exposed to a whole-head photon irradiation dose of 6 Gy (1). Five weeks after treatment, no significant difference in serum levels of pituitary hormones was found between the irradiated sample and the non-irradiated control group. However, after 20 weeks the irradiated group presented significantly lower levels of serum adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), and growth hormone (GH) compared to the controls (p < 0.001, p < 0.5, and p < 0.05, respectively). This delay emphasises the importance of long-term follow up in children who have undergone cranial RT, as it may take time for the adverse effects to develop. As the childrens’ bodies are developing, they are much more vulnerable to perturbations, therefore, early diagnosis is key in order to minimise detrimental health impacts such as stunted growth. Furthermore, on a cellular level they found evidence of a significant reduction in survival of proliferating cells within the pituitary gland as well as upregulation of both apoptosis and inflammation-related pathways after irradiation. This highlights that a 6 Gy dose in one fraction may be beyond the threshold for repair in some pituitary cells (1). Overall, this study by Xu et al. provides valuable information about the effects of radiation on cells within the pituitary gland, however, there are some limitations. Although 6 Gy provide a biologically effective dose equivalent to 12 Gy after daily repeated 2 Gy fractions (1), a single dose may not allow normal tissue to recover to the same extent as it would following standard fractionated treatment due to the increase in single and double strand breaks associated with a single higher dose. The implication of this is that the generated tissue damage and pathological effects may be slightly worse than would be seen in a clinical RT setting, therefore, it is not adequately representative of the effects seen in real-life paediatric RT. Additionally, as only female rats were used in this study, further research would require the inclusion of males in order to investigate whether or not there may be a difference between the genders.

In 2018, Vatner et al. investigated endocrine deficiency as a function of radiation dose to the hypothalamus and pituitary gland following proton beam RT in 189 patients aged < 26 years (10). Though this study included two patients with craniopharyngioma, it should be noted that these patients had no endocrine disruption at the time of irradiation. The results indicated that in addition to radiation
dose, age at the time of treatment and the time between end of treatment and study were also associated with an elevated risk of endocrinopathy in children who had undergone cranial irradiation. Out of the 189 patients, 48.8% developed at least one hormone deficiency, with the risk being higher in those treated between the ages of 6 to 10 years, compared to those < 6 years and > 10 years (10). This suggests the presence of a critical period in which the children are more vulnerable to the effects of radiation. Identifying the most sensitive age group may help reduce the risk of endocrinopathy when creating a RT treatment plan; methods such as hyperfractionation (delivering lower radiation doses in more sessions) may be favoured in order to try to spare as much of the HP-axis as possible. Although the benefit of hyperfractionation compared to standard treatment is controversial due to inconsistent results, more research in this area may be of value. Amongst all participants, GH deficiency was the most common at a rate of 37.4%. As GH is critical for normal growth and development, a deficiency can have significant impacts such as stunted growth, dwarfism, and obesity (9). Furthermore, TSH deficiency was the second most common endocrinopathy that manifested in 20.5% of patients, followed by ACTH deficiency in 6.9%. Luteinizing hormone and Follicle stimulating hormone (LH/FSH) deficiency was found in only 4.1% of the children following RT. In terms of dose response, 78.8% of those who developed a growth hormone deficiency received a dose \( \geq 40 \text{ Gy} \) to the HP-axis, whereas only 9% consist of individuals who received \( \leq 20 \text{ Gy} \) (10). This highlights that the total radiation dose is one of the main factors that increases the risk of endocrinopathy, as all fractions were delivered in 1.6 Gy doses. Although the authors found no significant contribution of chemotherapy to increasing the risk of endocrinopathy, the lack of clinical detail regarding the chemotherapy given to each patient (drug type, dose, number of cycles) prevents comparisons from being made to other studies where chemotherapy has been considered to be a contributor to endocrinopathy (11). Furthermore 83.6% of the participants were white, which creates a data gap that lacks representation of non-white races sufficiently and so further research including a more diverse sample would be beneficial.
Prevalence and Long-Term Follow-Up of Endocrine Deficiency

Hormone deficiencies are common amongst childhood cancer survivors and require treatment to minimise the effect on their quality of life. In 2015, Chemaitilly et al. published a report from the St Jude Lifetime Cohort Study investigating the prevalence and effects of untreated anterior hypopituitarism in 748 childhood cancer survivors who had undergone cranial irradiation (12). After a mean follow-up of 27.3 years, they found that 46.5% had developed GH deficiency, followed by 10.8% being deficient in the LH/FSH, 7.5% lacking TSH and lastly 4% suffering from ACTH deficiency. Out of the individuals suffering from GH and LH/FSH deficiency, 99.7% and 78.5% respectively were untreated (12), highlighting that vigilance for these late endocrine effects is below par. Untreated GH deficiency was found to be significantly correlated with reduced muscle mass and tolerance to exercise, and untreated LH/FSH deficiency was linked to hypertension, low bone mineral density, dyslipidemia, and slow walking. Additionally, both deficiencies were independently associated with muscle weakness, reduced energy expenditure, and obesity in the abdomen (12). These results provide evidence for the peripheral secondary effects which are induced following cranial irradiation and amplify the importance of sparing the HP-axis. Not only are the secondary effects likely to impact the patients’ quality of life but they may also further add to healthcare costs as anti-hypertensive drugs, for example, may also need to be administered. Notably, the most common doses received by 42.3% of the patients were 22-29.9 Gy, followed by 27.8% receiving 15-21.9 Gy (12). This emphasises that although the risk of endocrine deficiency increases with radiation dose, as demonstrated by Vatner et al. (10), endocrinopathy still occurs at relatively low radiation doses. A strength of this investigation is its long follow-up period which it accounts for the delayed onset of endocrinopathy as was observed in the rat model (1) and is important since the prevalence of hormone deficiency has been found to increase with time since last treatment (10). As a result, they were more likely to detect the late effects of cranial irradiation, rather than just the acute effects. Furthermore, as all the participants were treated at St Jude Children’s Research Hospital, it can likely be assumed that treatment procedures and equipment were relatively similar in all the children. However, a stark weakness is the lack of information regarding the RT treatments; Chemaitilly et al. do not mention the RT technique (i.e., IMRT, 3DCRT, or other), fractionation details, or how many were receiving concurrent chemotherapy or other treatment which may also influence the results. This information is critical when interpreting the results in order to identify factors that may potentiate damage and increase the risk of late endocrine deficiency.
Data from patients who had previously enrolled in the St Jude Lifetime cohort study was also utilised by van Iersel et al. in 2019 to investigate the prevalence of endocrine deficiency and their consequent health impacts in childhood cancer survivors (11). A strength of this study is that they also used data from children with brain tumours that had not undergone RT, allowing comparisons to be made between irradiated and non-irradiated patients. In the 1086 irradiated children, they found an estimated prevalence of 40.2% for GH deficiency, followed by 11.1% for TSH deficiency, 10.6% for LH/FSH deficiency, and a 3.2% prevalence of ACTH deficiency after a median follow up period of 24.1 years (11). In those who did not receive RT, only 6.2% developed GH deficiency and <1% developed other endocrinopathies. Overall, GH-, TSH- and LH/FSH hormone deficiencies were independently associated with RT to the HP-axis at any dose, and at > 30 Gy for ACTH deficiency (11). Furthermore, they found that GH deficiency was associated with short stature, low bone mineral density, poor tolerance to exercise, as well as frailty. TSH deficiency was also associated with short stature and poor tolerance to exercise, in addition to LH/FSH deficiency being linked to low bone mineral density and obesity (11). As all these adverse outcomes can have a substantial impact on the patients’ quality of life, early diagnosis and intervention is crucial to minimise the effects, emphasising the need for regular, long-term follow up. A drawback of the study was that out of the 1086 participants who had received cranial irradiation, dosimetry data for the HP-axis was only available for 921 of them. As a result, van Iersel et al. quantified the RT dose to the HP-axis as the "maximum tumour-prescribed dose to the brain" (11). This may produce an overestimation of the radiation dose required to induce a certain level of damage to the HP-axis and consequent hormone deficiency, as the actual dose that the HP-axis was exposed to may have been lower than the maximum. As with the study by Chemaitilly et al. (12), details regarding RT methods and treatment planning are not included, which may have been useful.

Similar results were reinforced in a more recent study by van Iersel et al. in 2020, which explored the impact of hypothalamic and pituitary disorders following high-dose conformal photon RT in 355 children with brain tumours, with a median follow-up period of 10 years (6). The median age at treatment was 6.4 years, and all patients received a total radiation dose between 50.4 – 59.4 Gy to the tumour volume. GH deficiency was again found to be most common, with a prevalence of 37.2%, as was observed by Vatner et al. (10). However, LH/FSH deficiency was found to be the second most common at 17.7%. TSH deficiency was the third most common, occurring in 14.9% of the children, followed by ACTH
deficiency in 10.3% of the irradiated children. These results differ from that of Vatner et al. (10) and the previous study by van Iersel et al. in 2019 (11), which could either be due to the individual differences in the samples, the follow-up periods, or due to the investigated total radiation dose being greater than the previous studies. Dose-dependence was also apparent as a mean dose to the hypothalamus of ≥ 36 Gy was associated with a greater risk of developing any endocrine deficiency. Additionally, GH deficiency was linked to both short stature and low bone mineral density (6), as observed in previous studies (11, 12). This provides further evidence to support the idea that childhood cancer survivors are plagued by late effects as a result of treatment, and emphasises the importance of early diagnosis, as immediate hormone replacement therapy may have prevented these clinical presentations.

Other risk factors associated with endocrine deficiency after RT

The combination of RT with other treatments such as chemotherapy may elevate the risk of developing hormone deficiencies. In the 2019 study, van Iersel et al. also found that disorder of the HP-axis was independently associated with intrathecal chemotherapy, alkylating agents, seizures, stroke, and hydrocephalus with shunt placement. These results highlight that RT may not be the only contributor to endocrinopathy in childhood cancer survivors, although it appears to be the most dominant factor. Seizures, strokes and hydrocephalus with shunt placement all involve some degree of damage to tissues of the CNS, which may be what leads to a disordered HP-axis. However, as noted by van Iersel et al., as it is uncertain whether these CNS insults preceded the onset of endocrinopathy, it cannot be assumed that there is a causal relationship (11).

Unlike many other studies, in the 2020 study by van Iersel et al, 64.5% of the children were not receiving concurrent chemotherapy. This left a big window of opportunity for comparison between children who had and had not received concurrent chemotherapy, which could have identified whether the combination of RT and chemotherapeutic drugs exacerbates damage to the hypothalamus and pituitary gland. Regrettably, the authors made no attempt at such comparison. Additionally, a race data-gap was also present in this study; although 14% were black, only 8.45% of participants were of “other” races, again highlighting the demand for further research into the effects in non-white races.
A fraction of this data-gap was covered in 2019 by Heo et al., who investigated the prevalence of endocrine disorders in childhood brain tumour survivors in South Korea (13). With a median follow-up period of 5 years, they found that 17.4% of the children were suffering from hypopituitarism. This data, however, also includes patients who were not treated with RT, allowing comparisons to be made between the two groups. They found that those who underwent RT were significantly more likely to develop an endocrine disorder compared to those who did not (p<0.001). This supports the notion that RT is most likely the main cause of post-treatment endocrine disorder, rather than chemotherapy or other treatments on their own, as suggested by van Iersel et al. (11). Nevertheless, it does not rule out the possibility that chemotherapy or other oncological treatments have combined action with RT, which may exacerbate the damage to healthy tissues. Furthermore, they found that both females and children diagnosed before the age of 10 were at most risk of developing a hormone deficiency (13). This reinforces the existence of a critical period in which the children are most vulnerable and stresses the need for treatment to be adjusted accordingly to prevent the late endocrine sequelae. Delaying RT by prioritising chemotherapy and other treatments until the child is outside of this critical period where possible may be beneficial. The difference in risk between the sexes is unlike the previous studies where no sex difference was established (6, 10, 11). There could be a genetic component involved which makes East-Asian women more at risk than their male counterparts which would not have been spotted in the studies by Vatner et al. (10) and van Iersel et al. (6,11) due to the vast majority of their subjects being white. The method used to gather data by Heo et al. was to collect data from the Korean National Health Insurance claims database to find children who had developed endocrine disorders after a brain tumour diagnosis (13). This is an imperfect method; firstly, it does not provide information about how many people had actually been tested for a hormone deficiency, therefore it does not account for individuals who may have an undiagnosed deficiency, which could mean that actual prevalence may be slightly higher than what has been calculated. Additionally, this method of data collection omits important clinical information that may be relevant when drawing conclusions from the data. For example, as we know nothing about the RT plans and radiation doses, it could simply be that the females in this sample had more severe tumours that required greater radiation doses, or tumours closer to the HP-axis, leading to an increased risk of endocrinopathy, as demonstrated by Vatner et al. (10).
A study by Patti et al. in 2020 revealed a new avenue of research relating RT, endocrinology, and the immune system in individuals with childhood-onset brain tumours. They investigated the presence of anti-pituitary and anti-hypothalamic autoantibodies in 46 irradiated children with craniopharyngioma, germinoma or gliomas (14). Measuring the levels of circulating autoantibodies targeting the HP-axis allowed for investigation of the immune system as a potential mediator in the development of endocrine disorder following RT, rather than looking only at RT and hormone deficiency as cause and effect. They found circulating anti-pituitary and anti-hypothalamus autoantibodies in 47.8% of these children, but none in the 50 healthy controls, with the presence of anti-pituitary antibodies being significantly associated with RT (p=0.03) (14). This implies that perhaps RT does not only cause direct damage to the pituitary gland, but it may also cause indirect damage by triggering an inappropriate immune attack on the pituitary tissues by the autoantibodies, subsequently leading to hypopituitarism. As this is novel research, it cannot be assumed that there is a direct causal relationship between RT and the release of autoantibodies. However, more research in this area could explore the potential of preserving the intracranial endocrine tissues by blocking this immune response using immunosuppressive drugs. This does present another trade-off between the benefits and risks of treatments as a functional immune system is critical to prevent proliferation of existing tumour cells, or the development of further neoplasms. On the other hand, the presence of these antibodies may simply be a regular immune response to the radiation-damaged cells in the pituitary gland following RT.

Discussion

This literature review summarises the current knowledge and understanding of the link between cranial RT and the development of endocrine deficiency in paediatric patients, with the aim of finding ways in which the research could be further improved. Several previous studies which are summarised in Table 2 have provided evidence that cranial irradiation is a risk factor for the development of endocrine deficiency, due to exposure of the HP-axis to radiation. Generally, GH deficiency tends to be the most common endocrinopathy, with a prevalence of up to 46.5% followed by either LH/FSH or TSH deficiency, with ACTH deficiency being the least common, except in the study by Vatner et al. (10) as shown in Figure 3. Although proton beam
RT has a negligible exit dose and has been described to have “substantial clinical advantage” compared to photon beam RT (15), the rates of endocrinopathy following proton beam RT were generally similar when compared to those treated using photons, unlike expected, as shown in Figure 3. This suggests that the entry dose is responsible for the damage to the tissues of the HP-axis, which is difficult to avoid if the tumour is proximal to the HP-tissues. Furthermore, the difference in the rates of LH/FSH and ACTH deficiency compared to the photon studies may suggest that there are differences in the sensitivities of the HP-axis tissues to different types of radiation. However, as only one study utilising proton beam RT met the criteria for this review, which had a much smaller sample size than the photon studies, further research in this area is needed for reasonable comparisons to be made.

Due to the challenging nature of this research, various limitations are apparent. Firstly, the use of retrospective data may allow confounding factors to influence the results. For example, there may be a difference between the use of neoadjuvant or adjuvant chemotherapy, or perhaps some chemotherapeutic drugs may increase radiation sensitivity of the HP-axis and therefore increase the risk of endocrinopathy. Additionally, the use of long-term retrospective data poses a trade-off. Although longer follow-up studies, such as the 27-year period accounted for by Chemaitilly et al. (12), ensure that late-onset endocrine sequelae are accounted for, they inevitably reflect the outcomes of older treatment techniques. On the other hand, studies such as that by Vatner et al. (10) with a median follow-up period of 4 years may offer a better reflection of modern treatment outcomes but come at the cost of potentially missing late-onset cases.

Furthermore, as outlined by van Iersel et al. in 2019, there are several other factors such as intrathecal chemotherapy and CNS insults that may be involved in potentiating damage to the HP-axis (11). This information is not always included in the data and thus is not often analysed, making it uncertain whether or not they may have an impact on the results. Moreover, other important clinical information, such as the RT planning techniques, were often omitted from the papers, preventing the identification of methods and dose distributions which may be more effective at sparing the endocrine tissues. Additionally, retrospective studies may allow for selection bias; it could be argued that individuals who suffer from more distinct and detrimental side effects are more inclined to participate in follow-up studies than those who were generally unaffected and are living normal lives. The implication of this is that the proportion
of individuals with severe complications in the studies may be greater than that of the general population of children who have undergone cranial RT. Furthermore, the apparent data-gap in representation of non-white races means that until this data is provided, it cannot be assumed that minorities experience the same effects as their well-studied white counterparts; they may perhaps be more or less resistant to radiation damage. Overall, there is ample room for further research; studies comparing different chemotherapies (different drugs, neoadjuvant or adjuvant, intrathecal etc.) and children treated with or without RT would allow us to more accurately identify individual risk factors. Moreover, comparisons between differently fractionated treatments, and between different RT beam types may unveil treatment methods that are more successful in sparing the intracranial endocrine tissues. Furthermore, FLASH-RT, which involves the use of ultra-high dose rates, has in several pre-clinical studies been shown to be effective in sparing healthy tissues (16). Though research is still in early stages, FLASH-RT may be a useful option in the future when it comes to sparing the endocrine system. Following on from the results produced by Patti et al. (14), future studies may want to consider antibody screening to establish whether or not autoimmune response is involved in the development of endocrine deficiency following cranial RT.

Conclusion

There is strong evidence to suggest that cranial irradiation is the main risk factor involved in the development of HP-axis dysfunction in childhood cancer survivors, with the risk being dose-dependent, greater in children between the ages of 6 to 10 years and increasing with time since last treatment. However, there are several other probable factors which may potentiate the damage, such as chemotherapy, CNS insults, and potentially the release of anti-pituitary antibodies. Therefore, more research is needed to narrow down the main mechanisms of destruction. As the onset of deficiency can be very late, it is crucial that childhood cancer survivors undergo long-term endocrine follow ups to try to get an early diagnosis and minimise further health complications. At this point in time, no obvious and universal solution to this problem is apparent; further investigation is needed to identify specific factors which could be manipulated to minimise the risk of late endocrine effects, potentially reducing total treatment costs, and improving the survivors’ quality of life. However, taking the factors that make an individual more vulnerable into consideration when planning treatment may be one way forward to help reduce the risk of radiation damage to the HP-axis and thus hormone deficiency.
Conflicts of Interest: There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding: Professor Marcel van Herk was supported by the National Institutes of Health Research of Manchester Biomedical Research Centre. Abigail Bryce-Atkinson was sponsored by a SU2C-CRUK Pediatric Cancer New Discoveries Challenge Team Grant (Grant Number: SU2C#RT6186). This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements: Thank you to Nathalie Lövgren for proofreading the original text.

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**Figure 1. The Intended Effect of Radiation on a Tumour Cell.** Radiation exposure often causes DNA strand breaks in the tumour cell, typically leading to cell death (3). Figure created with BioRender.com.

**Figure 2. Summary of Key Hormones of the Hypothalamic-Pituitary (HP) Axis, Their Functions, and the Known Consequences of Their Absence.** (A) Thyroid Stimulating Hormone (TSH) released from the pituitary gland stimulates triiodothyronine release ($T_3$) from the thyroid gland. (B) Adrenocorticotropin (ACTH) released from corticotropes in the pituitary gland acts on the suprarenal adrenal glands, stimulating release of cortisol. (C) Growth Hormone (GH) from the pituitary acts on the liver to stimulate release of Insulin-like Growth Factor 1 (IGF-1). (D) Gonadotropic cells in the pituitary release Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH), which act on the testes and ovaries to release reproductive hormones. Information summarised from White et al. (9). Figure created with BioRender.com.
Figure 3. The Prevalence of Hormone Deficiency in Childhood Cancer Survivors Following Cranial Irradiation. GH = Growth hormone, TSH = Thyroid stimulating hormone LH/FSH = luteinizing and follicle stimulating hormone, and ACTH = adrenocorticotropic. “Photon” indicates the use of photon-beam RT, and “Proton” refers to proton-beam RT.
Table 1: Prevalence of Intracranial Paediatric Tumours. Information from Dang & Philips (2).

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### Table 2: Recent Publications on the Effects of Radiotherapy on the HP-axis in Paediatric Patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Measured outcome</th>
<th>Population</th>
<th>n</th>
<th>Age at Treatment</th>
<th>RT Treatment</th>
<th>Radiation Dose</th>
<th>Follow-up Period</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu et al., 2020 (1)</td>
<td>Serum GH, TSH, and ACTH</td>
<td>Female Wistar rats</td>
<td>40</td>
<td>11 Days</td>
<td>Whole-head photon-beam RT</td>
<td>6 Gy</td>
<td>20 Weeks</td>
<td>- Lower serum levels of ACTH, TSH and GH 20 weeks post-RT (p&lt;0.001, p&lt;0.5, and p&lt;0.05 respectively).</td>
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<tr>
<td>Vatner et al., 2018 (10)</td>
<td>Serum GH, TSH, ACTH, and LH/FSH</td>
<td>Brain tumour patients</td>
<td>189</td>
<td>&lt;26 years</td>
<td>3D conformal proton-beam RT: Median hypothalamus dose: 26 Gy. Median pituitary dose: 24.3 Gy</td>
<td>Median 4.4 years</td>
<td>- 48.8% developed at least one deficiency. - Radiation dose, age at treatment, and time between end of treatment and study associated with an elevated risk of hormone deficiency.</td>
<td></td>
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<tr>
<td>Chemaitilly et al., 2015 (12)</td>
<td>Serum GH, TSH, ACTH, and LH/FSH</td>
<td>Brain tumour patients</td>
<td>748</td>
<td>&lt;26 years</td>
<td>Median cranial RT dose: 22-29.9 Gy.</td>
<td>Mean 27.3 years</td>
<td>- GH-deficiency most common, followed by LH/FSH-, TSH-, and ACTH-deficiency. - 99.7% and 78.5% of the GH- and LH/FSH- deficient patients were untreated.</td>
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<tr>
<td>van Iersel et al., 2019 (11)</td>
<td>Serum GH, TSH, ACTH, and LH/FSH</td>
<td>Brain tumour patients</td>
<td>1086</td>
<td>&lt;18 years</td>
<td>Median HP dose: 20-30 Gy.</td>
<td>Median 24.1 years</td>
<td>- GH-, TSH-, and LH/FSH deficiencies independently associated with RT to the HP-axis at any dose, and ACTH at doses &gt; 30 Gy.</td>
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<tr>
<td>van Iersel et al., 2020 (6)</td>
<td>Serum GH, TSH, ACTH, and LH/FSH</td>
<td>Brain tumour patients</td>
<td>355</td>
<td>&lt;24.9 years</td>
<td>High dose conformal and intensity-modulated photon-beam RT Total dose range: 50.4-59.4 Gy. Median hypothalamus dose: 23.4-36 Gy.</td>
<td>Median 10 years</td>
<td>- GH-deficiency most common followed by LH/FSH-, TSH-, and ACTH-deficiency.</td>
<td></td>
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<tr>
<td>Heo et al., 2019 (13)</td>
<td>Incidence of hypopituitarism</td>
<td>Brain tumour patients</td>
<td>1058</td>
<td>&lt;18 years</td>
<td></td>
<td>Median 5 years</td>
<td>- Irradiated patients significantly more likely to develop hypopituitarism than non-irradiated counterparts (p&lt;0.001). - Females and children diagnosed with cancer &lt;10 years of age most at risk.</td>
<td></td>
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<tr>
<td>Patti et al., 2020 (14)</td>
<td>Serum AHA, APA, GH, TSH, LF/FSH, and ACTH levels</td>
<td>Brain tumour patients</td>
<td>46</td>
<td>Median age: 13 years</td>
<td></td>
<td>Median 5 years</td>
<td>- 47.8% of irradiated group had circulating APAs. - RT significantly associated with presence of APAs (p=0.03)</td>
<td></td>
</tr>
</tbody>
</table>

Anti-hypothalamus autoantibodies (AHA), anti-pituitary autoantibodies (APA). Dashes indicate where no clinical information was provided.
Radiation Beam → DNA Breaks in Tumour Cell → Cell Death
**Actions:**
- ↑ cardiac output
- ↑ basal metabolic rate
- ↑ heat production
- ↑ sympathetic nervous system activity
- ↑ linear growth of bone and maturation of epiphyseal bone centres

**Consequences of hypothyroidism:**
Goitre, low metabolic rate, weight gain, ↓ cardiac output, muscle pain, weakness, anaemia

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**IGF-1**

**Actions:**
- ↑ blood glucose
- ↑ lipolysis
- ↑ Protein synthesis
- ↑ DNA synthesis
- ↑ Cell size and number
- ↑ Cartilage growth
- ↑ Long bone growth

**Consequences of growth hormone deficiency:**
Stunted growth, dwarfism, obesity, hypoglycaemia, decreased muscle mass

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**Cortisol**

**Actions:**
- ↑ blood glucose
- Glycogenic
- Gluconeogenic
- Anti-inflammatory
- Suppression of immune system
- ↑ vascular response to catecholamines

**Consequences of hypoadrenalism:**
Weakness, hypoglycaemia, weight loss, anorexia, psychosis, hypotension

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**HP-Axis**

**Actions:**
- Stimulation of bone growth
- Stimulation of growth, development and function of male and female genitalia
- Regulate the menstrual cycle
- Induces puberty

**Consequences of hypogonadism:**
Infertility, delayed puberty, late closure of epiphyseal bones, bone loss, amenorrhea, impotence

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