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PENTEC ORGAN SYSTEM REVIEW

Central Endocrine Complications Among Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review

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Purpose: Children who receive cranial radiation therapy (RT) as a component of treatment for malignancy are often at risk of long-term central endocrine toxicity secondary to radiation to the hypothalamic-pituitary axis (HPA). A comprehensive analysis was performed of central endocrine late effects in survivors of childhood cancer treated with RT as part of the Pediatric Normal Tissue Effects in the Clinic (PENTEC) consortium.

Methods and Materials: A systematic review of the risk of RT-related central endocrine effects was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A total of 4629 publications were identified, of which 16 met criteria for inclusion in dose modeling analysis, with a total of 570 patients in 19 cohorts. Eighteen cohorts reported outcomes for growth hormone deficiency (GHD), 7 reported outcomes for central hypothyroidism (HT), and 6 reported outcomes for adrenocorticotropic hormone (ACTH) deficiency.

Results: Normal tissue complication probability modeling for GHD (18 cohorts, 545 patients) yielded D_{50} = 24.9 Gy (95% CI, 20.9-28.0) and γ_{50} = 0.5 (95% CI, 0.27-0.78). The normal tissue complication probability model fit for whole brain irradiation

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in children with a median age of >5 years indicated a 20% risk of GHD for patients who receive a mean dose of 21 Gy in 2-Gy fractions to the HPA. For HT, among 7 cohorts (250 patients), D_{50} = 39 Gy (95% CI, 34.1-53.2) and γ_{50} = 0.81 (95% CI, 0.46-1.35), with a 20% risk of HT in children who receive a mean dose of 22 Gy in 2-Gy fractions to the HPA. For ACTH deficiency (6 cohorts, 230 patients), D_{50} = 61 Gy (95% CI, 44.7-119.4) and γ_{50} = 0.76 (95% CI, 0.5-1.19); there is a 20% risk of ACTH deficiency in children who receive a mean dose of 34 Gy in 2-Gy fractions to the HPA.

Conclusions: RT dose to the HPA increases the risk of central endocrine toxicity, including GHD, HT, and ACTH deficiency. In some clinical situations, these toxicities may be difficult to avoid, and counseling of patients and families with respect to anticipated outcomes is important. © 2023 Elsevier Inc. All rights reserved.

Introduction

Radiation therapy (RT) is an integral component of the treatment paradigm for many pediatric malignancies. One-third of all pediatric cancers will require RT as part of their treatment, and their curability (and thus longevity) mandates consideration of the long-term treatment-related toxicities.[1] Toxicity associated with RT to the hypothalamic-pituitary axis (HPA) can dramatically impact health and quality of life and causes multiple downstream effects. A comprehensive review of the literature on pediatric cancer survivors who received RT exposing the HPA was performed as part of the Pediatric Normal Tissue Effects in the Clinic (PENTEC) project. Data were used to create normal tissue complication probability (NTCP) models for central endocrinopathies resulting from RT, including growth hormone deficiency (GHD), central hypothyroidism (HT), and adrenocorticotropic hormone (ACTH) deficiency.

Clinical Significance

The HPA is routinely exposed to therapeutic doses of RT in many clinical scenarios, including RT to the whole brain (eg, leukemias), craniospinal axis (eg, medulloblastomas and nongerminomatous germ cell tumors), total body (eg, before stem cell transplantation), hypothalamus or pituitary itself (eg, craniopharyngiomas, optic gliomas, hypothalamic astrocytomas), and whole ventricular system (eg, germinomas). Further, in patients receiving RT for other central nervous system or head and neck tumors (eg, ependymomas, gliomas, rhabdomyosarcomas, esthesioneuroblastomas, retinoblastomas), the HPA may be exposed to significant doses depending on the size, shape, and location of the tumor.

With the advent of megavoltage RT and standardized treatment paradigms for pediatric malignancies, the first generation of brain tumor survivors treated with RT emerged in the late 1960s and 1970s. The first series documenting endocrinopathies were published in the 1970s.[2,3] These endocrinopathies were found to be dose dependent, with GHD representing the most common (occurring even after lower doses), and deficiencies of thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), and ACTH occurring with higher doses.[4,5] The cause of hormone deficiencies may be multifactorial, with surgery and hydrocephalus also being potential contributing factors. The neurohypophysis (ie, the posterior pituitary) appears to be less vulnerable to radiation-induced toxicity, with the vast majority of diabetes insipidus cases being caused by surgery or direct tumor effects, and rarely by RT.[6]

GHD results in reduced growth velocity in prepubertal children and without intervention results in permanent short stature once the bones reach maturity during puberty. It also results in an increase in centripetal body fat, reduction in lean muscle mass, osteoporosis (reduced bone mineral density), reduced muscle strength, lipid abnormalities such as increased low-density lipoprotein cholesterol, insulin resistance, impaired cardiac function, and fatigue.[7] Fatigue due to GHD is difficult to diagnose, as brain tumor survivors may have chronic fatigue as a result of the cranial irradiation itself.[8] Most of these GHD-related complications are alleviated by prompt diagnosis and treatment with recombinant growth hormone. Available data suggest that recombinant growth hormone administration does not result in increased malignancies in those patients requiring replacement.[9]

Central HT from RT is diagnosed by low TSH levels in the setting of low circulating thyroxine and triiodothyronine levels.[10] Clinically, this manifests in weight gain, cold intolerance, fatigue, hair changes, and somnolence. It also can cause dramatic elevation of cholesterol levels. This constellation of effects also aggravates the cardio/cerebrovascular complications from both metabolic syndrome and the direct effects of RT. Management involves oral replacement therapy and regular blood level monitoring to stabilize the replacement therapy dose.[11]

ACTH deficiency results in the reduction of production of systemic corticosteroids.[12] This may be reflected in an Addison syndrome with hyponatremia, hyperkalemia, and hypotension. Fatigue may also be a presenting symptom. In milder cases, there is an acute deterioration in times of physiological stress and a slow resolution of infective illnesses. In the more severe cases, replacement of both mineralocorticoid (fludrocortisone) and corticosteroid (hydrocortisone) is needed; milder cases require ongoing hydrocortisone or hydrocortisone dosing with stress (eg, operations or infections).[13,14]

Gonadotrophin effects from RT may present as precocious puberty or hypogonadism. Hypogonadism prepubertally presents as pubertal delay with lack of growth and lack of secondary sexual characteristics. In postpubertal patients,

hypogonadism manifests as amenorrhea, infertility, erectile dysfunction, and vasomotor symptoms. Management involves hormonal replacement therapy in both sexes. To regain fertility, gonadotropin-releasing hormone agonists can be used in an effort to stimulate the production of gonadotrophs by the pituitary.[15]

Metabolic syndrome is characterized by weight gain (specifically central obesity), late satiety, glucose intolerance, and hypertension.[16] Both surgery and RT to the hypothalamus, and their associated endocrinopathies, can lead to metabolic syndrome,[17,18] with higher rates when both modalities are used. The clinical features of metabolic syndrome aggravate other late effects that affect the cardiovascular/cerebrovascular systems, such as ischemic heart disease, congestive cardiac failure, and stroke risk.

Endpoints

In the literature search and data aggregation for endocrine complications after RT to the HPA, data were available to analyze 3 primary endpoints: the dose-effect relationships between RT and GHD, HT, and ACTH deficiency. There was variability in toxicity reporting of these outcomes, leading to difficulty in data aggregation. Thresholds and definitions of deficiency for each hormone studied often varied by report. For the purposes of this analysis, severe deficiency in hormone status was defined as per each individual publication, as many reports did not specify quantitative hormone levels or quantify the severity of deficiency.

Anatomy and Developmental Dynamics

The pituitary gland sits in the hypophyseal fossa of the sphenoid bone in the center of the middle cranial fossa, surrounded by the sella turcica. The anterior lobe is responsible for production of hormones regulating growth, metabolism, stress, reproduction, and lactation. The middle lobe, which in humans is very small, produces melanocyte-stimulating hormone, and the posterior lobe (neurohypophysis) regulates sodium/fluid levels through the production of antidiuretic hormone. The pituitary receives trophic hormones from the hypothalamus, which sits at the base of the brain underlying the thalamus. The hypothalamus responds to both systemic levels of end organ hormones and neural stimuli from the central nervous system.

Embryologically, the anterior lobe forms from Rathke's pouch, which is an invagination of the oral ectoderm, and the posterior lobe derives from the diencephalon (neural ectoderm)[19-21] where it makes contact with Rathke's pouch.[22] Multipotent stem cells develop into thyrotrophs (responsible for TSH production), somatotrophs (growth hormone), gonadotrophs (FSH and LH), lactrotrophs (prolactin), and corticotrophins (ACTH).[23] Homeostasis is achieved through feedback from peripheral endocrine organs to the hypothalamus, which produces releasing hormones responsible for the size of these trophic cell populations, thus controlling the hormone expression and release from these cells.[22] These trophic factors travel from the hypothalamus to the pituitary via the hypophyseal portal blood vessels.[19] The posterior lobe of the pituitary (neurohypophysis) is distinct from the anterior lobe and is responsible for the release of oxytocin and vasopressin, which regulate lactation and osmotic balance, respectively.[24]

In early childhood, nutritional status is the major factor determining growth. From the age of 3 years until puberty, growth hormone and thyroxine are the major drivers of growth.[25]

During puberty, the average growth velocity nearly doubles, owing to a greater pulse amplitude and growth hormone secretion related to the activation of the hypothalamic-pituitary-gonadal axis by testosterone in males and estrogen in females. There is also a concomitant reduction in sensitivity of the hypothalamus to rising insulin-like growth factor 1 levels and greater sensitivity peripherally to growth hormone actions.[26] Once final height is attained, there is a drop off in growth hormone secretion by 20 years of age to about 25% of the peak levels in puberty.[27]

In adult men, growth hormone secretion is correlated with testosterone production and decreases with age. Postmenopausal women have lower growth hormone production than do premenopausal women, with growth hormone levels doubling during the late follicular phase. Decreased growth hormone production is also somewhat correlated to increases in total and visceral fat as well as declining physical fitness.[28,29]

In infants, the hypothalamic pituitary axis is immature, and the production of gonadotrophs is not responsive to peripheral sex hormone levels. In the first 2 years of life, the responsiveness of the hypothalamus is established, although the threshold of sensitivity remains high, and thus sex steroid and gonadotrophin levels in the blood remain low. During puberty, there is a reduction in the threshold of sensitivity to feedback, resulting in increased levels of sex steroids. The gonads also become more sensitive to gonadotrophs during this time.

Defining Volumes: Challenges and Assumptions

The hypothalamus and pituitary volumes can be defined on the radiation planning computed tomography scan, with more accuracy provided with use of a contrast-enhanced magnetic resonance imaging scan, which is generally a T1-weighted scan with gadolinium. For contouring of the whole pituitary gland, contrast may not be necessary, as the sella can be well visualized without contrast. Some of the studies reviewed here did not describe the specific dose to the hypothalamus and pituitary regions. In studies of whole brain radiation, the doses to the hypothalamus and pituitary were assumed to equate to the dose prescribed to the whole brain. Because of the very close proximity of the hypothalamus

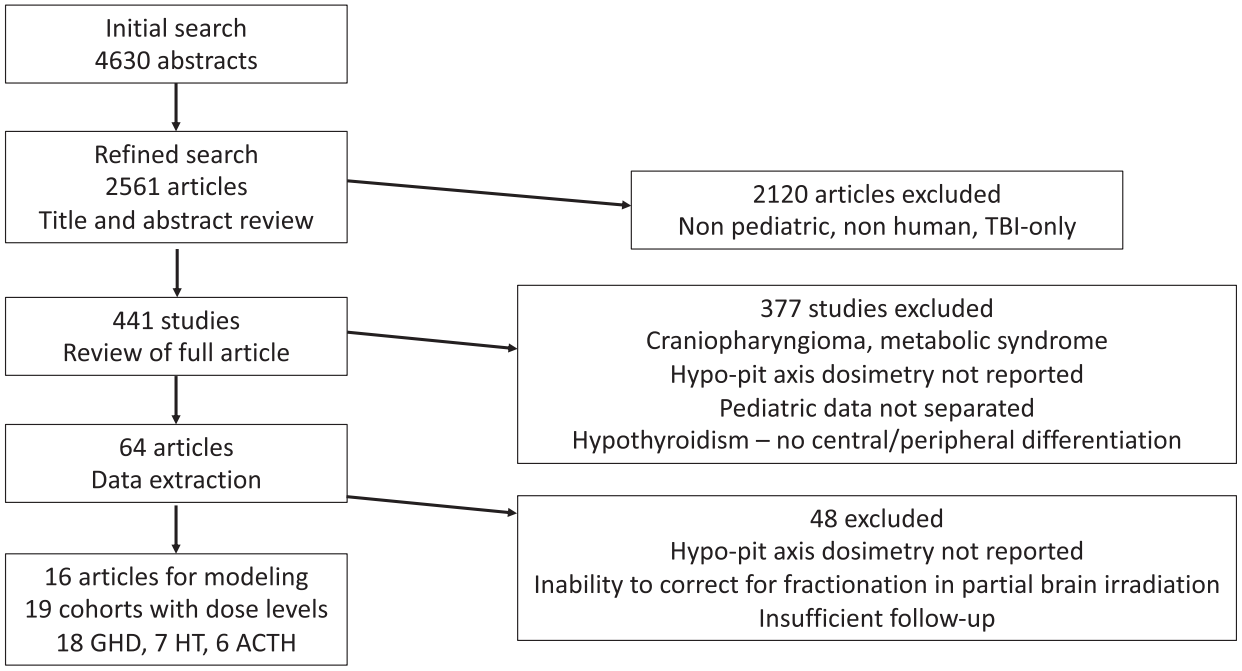

Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of study selection for analysis. *Abbreviations:* ACTH = adrenocorticotropic hormone (deficiency); GHD = growth hormone deficiency; HT = central hypothyroidism; TBI = total body irradiation.

and pituitary, the doses to both were assumed to be the same, unless otherwise specified.

Review of Dose-Volume Response Data and Risk Factors

Search methodology

The PENTEC systematic review of the risk of radiation-related central endocrine effects of childhood cancer treatment was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[30] A comprehensive search strategy was developed by GW, MD, JS, AK, & FD. The search included terms for cancer, childhood, RT, and central endocrine effects (see Appendix E1 for full search strategy). MEDLINE and Embase were searched for all peer-reviewed publications between 1950 and January 2017. Titles and abstracts were reviewed by GW, MD, KW, PD, BC, BA, MZ, TK, & EK. Full text was retrieved for all papers that any reviewer considered potentially eligible. Eligible studies were published as peer-reviewed papers, conducted in humans, published in English, included participants irradiated in childhood to the head, neck, or total body, and reported central endocrine effects. Owing to the length of the project, periodic searches were performed until June 2022 to maximize and update data collection. For eligible studies, GW, MD, KW, PD, BC, BA, MZ, TK, SH, & EK extracted data on study design, radiation treatment, patient characteristics, and central endocrine outcomes. Two reviewers extracted data for each study independently, and discrepancies were resolved by GW, JS, & KW.

Search results

The literature search identified 4629 unique references (Fig. 1). After discussion with the team, a refined search identified 2561 unique references, of which 2120 were excluded based on a review of titles and abstracts. The 441 references remaining were assessed for reporting of dosimetric data to the HPA, exclusive inclusion of pediatric patients or ability to independently assess pediatric patients, clearly defined endocrine outcomes, and confounding factors.

After discussion among the task force members and with the PENTEC steering committee, publications reporting the following topics were excluded: metabolic syndrome, GHD defined by height criteria only, endocrine outcomes exclusively following total body irradiation (for which all extracranial endocrine organs are irradiated), thyroid deficiency not specified by central or primary etiology, and endocrinopathies among those with HPA tumors (eg, craniopharyngiomas and some germinomas). Sixty-four remaining papers reported central endocrine effects of RT for childhood cancer and were submitted for data extraction. Of these, another 48 were excluded because the dose to the HPA could not be determined or corrected for fractionation, or because of insufficient patient follow-up. Specifically, 8 papers were excluded because they reported primarily non-central endocrine data, 9 papers were excluded because they only reported growth and height data, 8 papers were

excluded because they had incomplete data, 12 papers were excluded because of a lack of dose and/or fractionation data, 13 papers were excluded because of confounding radiation therapy administered (such as total body irradiation), 4 papers were excluded because of lack of follow-up, and 6 papers were excluded because of use of a similar and likely overlapping patient cohort to another study used in the present analysis.

The remaining 16 papers were included in this review and provided 19 separate cohorts with individual dose levels and toxicity scoring. Table 1 summarizes the included studies and cohorts. There were 570 patients included in these 19 cohorts. Eighteen cohorts reported GHD outcome, 7 reported HT outcome, and 6 reported ACTH deficiency outcome. Median doses in the cohorts ranged from 16.7 to 44.4 Gy in 2-Gy equivalent doses. Weighted median follow-up was 5.7 (range, 3.9-17.8) years (Table 1). Dosimetric uncertainties (Table 1) were estimated based on the totality of published information on a given study including, in some circumstances, associated papers from the same group of authors. In general, considered were time period, treatment technique, dose calculation methods including computer methods where applicable, equipment used for delivery, and other details that were given concerning dosimetry. The dose uncertainty was estimated for the organ of interest for the study, not necessarily for the whole target volume in the treatment (Table E1).

Mathematical models for dose-effect relationship

Models were developed for the outcomes of GHD, HT, and ACTH deficiency as function of dose to the HPA. Owing to the very similar dose to hypothalamus and pituitary gland, either reported dose was deemed acceptable for modeling. Only studies were included in which the dose to the HPA could be corrected for fractionation: all doses were converted into the equivalent dose with 2 Gy per fraction (EQD2) using the linear-quadratic model and an α/β ratio of 3 Gy.

Sample means and standard deviation for the cohorts were derived using a method proposed by Luo et al, which takes sample range, interquartile range, and cohort size into account.[47] An additional dosimetric uncertainty was applied depending on the age of the study and technique used; see Table 1 for estimated sample means, standard deviations, and dose uncertainties. In all presented figures, the dose error bars (horizontal axis) represent the standard deviation of the reported doses for each cohort, convolved with the dose uncertainties, assuming normality (ie, their variances summed up). The toxicity error bars (vertical axis) represent the binomial 95% CIs.

A logistic model with dose as a covariate was used to model the incidence of neuroendocrine sequelae as a function of mean EQD2 to the HPA:

$$NTCP = \frac{1}{1 + exp\left[4 \cdot \gamma_{50}\left(1 - \frac{EQD2}{D_{50}}\right)\right]}$$

To determine model parameters and confidence intervals, we used a combination of Monte Carlo and bootstrap methodology. First, a random number generator was used to generate 100 artificial cohorts with 570 patients each, drawn from the 19 cohorts listed in Table 1, using the available mean, standard deviation, and incidence of toxicity.

Subsequently, 1000 bootstrap cohorts were generated from each of the 100 artificial cohorts, using random sampling with replacement, yielding a total of 10^5 individual cohorts. Each of these cohorts was individually fitted using the model, and the distribution of the 10^5 best fit parameters allowed estimation of the 95% CIs for dose leading to 50% complication rate (D_{50}), normalized slope of the dose-response relationship (γ_{50}), and the fitted curves. All analyses and model fitting were performed in R, version 4.1.0, using the *stats* package.[48]

Risk factors

Multiple studies reported a strong dependence of the risk of injury on age at RT. For the GHD endpoint, for which the largest amount of data was available, a subgroup analysis was performed for cohorts where the patients' median age was >5 years. The few studies that investigated endocrine toxicity at multiple time points reported increasing rates of toxicities during the initial few years post-RT, with a slow stabilization of rates at 3 to 5 years.[42,49] Thus, 1 study was excluded that had only 2 years of follow-up.[50]

Dose-Volume and Outcome Associations

GHD

GHD data were available for 18 cohorts, representing a total of 545 patient outcomes. The weighted median age among these 18 cohorts was 6.5 (range, 3.1-8.7) years, and the weighted median follow-up among was 6.3 (range, 3.9-17.8) years. The best fit estimate of the NTCP model for all cohorts reporting GHD is shown as a full black line in Fig. 2A, with parameter estimates of D_{50} = 24.9 Gy (95% CI, 20.9-28.0) and γ_{50} = 0.5 (95% CI, 0.27-0.78). Restricting the fit to cohorts with median age over 5 years (12 cohorts, 431 patients, blue symbols) leads to a slightly higher estimate of D_{50} = 27.2 Gy (95% CI, 24.6-30.0) and a steeper dose response curve with γ_{50} = 0.83 (95% CI, 0.46-1.34); see dotted black line in Fig. 2A.

When further restricting the fit to only studies involving whole brain RT (7 cohorts, 178 patients total), where the dose to the HPA region is well known and homogeneous within each cohort, the dose-response curve further steepens (Fig. 2B; D_{50} = 25.6 Gy [23.7-31.6], γ_{50} = 1.75 [0.81-3.9]). This is because the patients in these cohorts all received the same dose (within our uncertainty estimate), and the partial brain cohorts in Fig. 2A add significant noise to the fit.

The NTCP model fit for whole brain RT in children with median age >5 years suggests a 20% risk of GHD for patients

Table 1 Data used in normal tissue complication probability model fitting

First study author and year	No.	Diagnosis	Median follow-up (y)	Median age (y)	Whole brain RT only	Mean EQD2± SD (Gy, $\alpha/\beta = 3$)	Estimated dose uncertainty (%)	Percentage with central hypothyroidism	Percentage with growth hormone deficiency	Percentage with adrenocorticotropic deficiency
Rohrer 2009[31]	20	Primary BT	12	3.6*	N	39.7 ± 7.6	15	55%	85%	20%
Schmiegelow 2000[32]	73	Primary BT	11	8.7	N	44.4 ± 12.5	10	-	80%	-
Laughton 2008[33]	88	Embryonal BT	4	7.3*	N	36.9 ± 5.0	5	65%	94%	38%
Logghe 1998 (1*)[34]	13	ALL	7	6.0*	Y	18.0	10	-	23%	-
Logghe 1998 (2*)[34]	21	ALL	7	6.0*	Y	24.0	10	-	61%	-
Voorhess 1986[35]	25	ALL	5	-	Y	24.0	10	3%	-	0%
Birkebaek 1998[36]	18	ALL	14	4.3*	Y	22.4	10	0%	50%	0%
Brauner 1986[37]	46	ALL	5	6.0	Y	24.0	10	-	39%	-
Cicognani 1992[38]	28	ALL	12	3.1*	Y	17.3	10	-	64%	-
Hata 2001[39]	20	ALL	6	6.8	Y	16.7	10	10%	5%	5%
Goddard 1999[40]	13	Orbital/parameningeal sarcoma	7	6.4*	N	37.3 ± 7.3	10	-	62%	-
Heikens 1998[41]	20	MB	16	8.0	N	30.8 ± 4.1	10	15%	35%	-
Yock 2016[42]	59	MB	5	6.6	N	29.5 ± 12.5	4	21%	46%	9%
Kirk 1987[43]	46	ALL	7	5.2*	Y	22.1	10	-	15%	-
Melin 1998[44]	35	ALL	5	3.7	Y	18.0	10	-	63%	-
Shalet 1976 (1*)[2]	5	ALL	4	3.4	Y	20.2	10	-	0%	-
Shalet 1976 (2*)[45]	8	ALL	5	4.5	Y	27.5	10	-	50%	-
Brennan 1998 (1*)[46]	11	ALL	18	6.9*	Y	17.3	10	-	0%	-
Brennan 1998 (2*)[46]	21	ALL	18	6.9*	Y	24.0	10	-	43%	-

All data are average values in the patient population as reported in each study or calculated from the reported data. Standard deviation for dose only reported for studies with variable doses. In cohorts that received partial brain radiation therapy with varying doses, the mean dose to the hypothalamic-pituitary axis is usually given.

Abbreviations: ALL = acute lymphoblastic leukemia; BT = brain tumor; EQD2 = estimated dose in 2 Gy per fraction; MB = medulloblastoma; N = no; Y = yes.

* Median age given at time of radiation therapy when possible, except for studies indicated with (*), for which only age at diagnosis was provided.

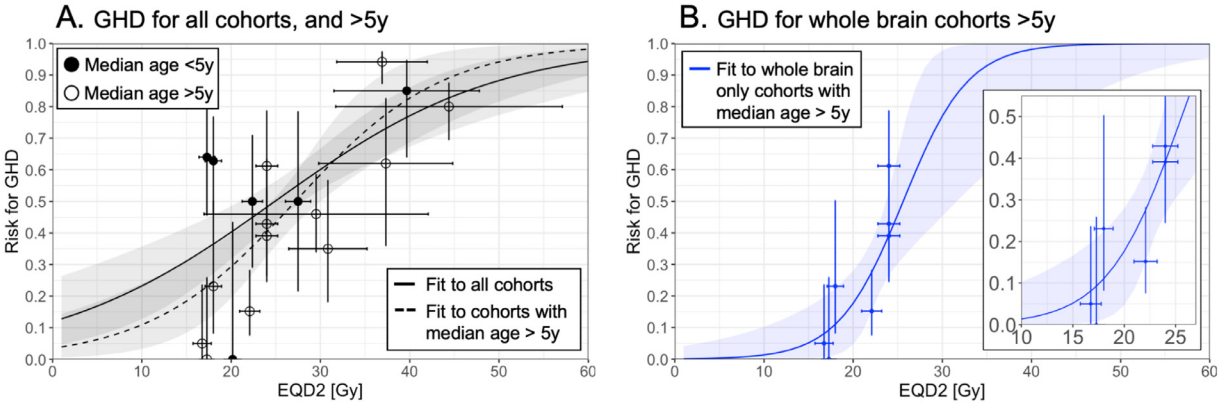

Fig. 2. Risk of GHD after radiation therapy to hypothalamus/pituitary region described using a logistic normal tissue complication probability model fitted to reported data in Table 1. (A) Full black line represents fit to all cohorts (best parameter fit estimates: D_{50} = 24.9 Gy [95% CI, 20.9-28.0], γ_{50} = 0.5 [95% CI, 0.27-0.78]). Dotted black line represents fit to all cohorts with median age >5 years (open symbols; best parameter fit estimates: D_{50} = 27.2 Gy [95% CI, 24.6-30.0], γ_{50} = 0.83 [95% CI, 0.46-1.34]). (B) Only cohorts receiving whole brain radiation therapy and median age >5 years (best parameter fit estimates: D_{50} = 25.6 Gy [23.7-31.6], γ_{50} = 1.75 [0.81-3.9]). Inset shows relevant dose range from 10 to 25 Gy EQD2. Shaded area represents 95% CI of model fits. Each cohort in Table 1 is represented by a data point; the X error bars represent the total standard deviation (a convolution of the dose variance within the cohort with the estimated dosimetric uncertainty), and the Y error bars represent the binomial 95% CI. *Abbreviations:* EQD2 = equivalent dose with 2 Gy per fraction, using α/β ratio = 3; GHD = growth hormone deficiency.

who receive 21 Gy in 2-Gy fractions to the HPA, increasing above that dose level (Table 2). The whole brain model is based on 178 patients, and owing to the known dose to the HPA axis in each cohort, the uncertainties estimated by the fit are narrow. Because of the underlying data (ie, exact same dose and known incidence for each data point) and our fitting method, the resulting fit and estimated uncertainty are comparable to what would be found if the patient-level dose and incidence data of these 178 patients were available.

Central HT

For HT, outcomes were available for 7 cohorts (250 patients), shown together with best fit estimates (D_{50} = 39 Gy [95% CI, 34.1-53.2], γ_{50} = 0.81 [95% CI, 0.46-1.35]) in Fig. 3A. The analysis suggests a 20% risk of HT in children who receive 22 Gy in 2-Gy fractions to the HPA. Restricting the fit to only cohorts with median age >5 years (212 patients, open symbols, dotted line) only changes the fit minimally.

ACTH deficiency

Figure 3B shows available ACTH deficiency outcomes (6 cohorts, 230 patients) together with the model's best fit estimates (D_{50} = 61 Gy [95% CI, 44.7-119.4], γ_{50} = 0.76 [95% CI, 0.5-1.19]). The NTCP model suggests a 20% risk of ACTH deficiency in children who receive 34 Gy in 2-Gy fractions to the HPA. Similar to the HT model, the fit only changes minimally when restricting the model to cohorts above 5 years median age (192 patients, open symbols, dotted line; for detailed fit parameters, see legend).

Table 2 Estimated incidence of GHD for WB-RT in cohorts with median age >5 years, derived from best fit estimate in Fig. 2B (D_{50} = 25.6 Gy, γ_{50} = 1.75)

Dose level (EQD2)	Estimated GHD incidence for WB-RT in patients >5 y	Estimated % change in GHD incidence per Gy
12 Gy	2.3% (95% CI, 0-12)	0.6% (95% CI, 0.02-1.3)
15 Gy	5.1% (95% CI, 0-17)	1.4% (95% CI, 0.1-2.1)
18 Gy	11% (95% CI, 2-23)	2.7% (95% CI, 0.9-3.6)
24 Gy	39.2% (95% CI, 27-53)	6.5% (95% CI, 2.3-15.5)
36 Gy	94.6% (95% CI, 62-100)	1.4% (95% CI, 0.04-3.1)

The right column describes the expected absolute change in GHD incidence per Gy_{EQD2} around each dose level to the hypothalamic-pituitary axis, according to the best fit estimate in Fig. 2B. The confidence intervals of the last column were estimated using all combinations of D_{50} and γ_{50} evaluated in the 10^5 individual fits at the respective doses, explaining their width.

Abbreviations: EQD2 = estimated dose in 2 Gy per fraction; GHD = growth hormone deficiency; WB-RT = whole brain radiation therapy.

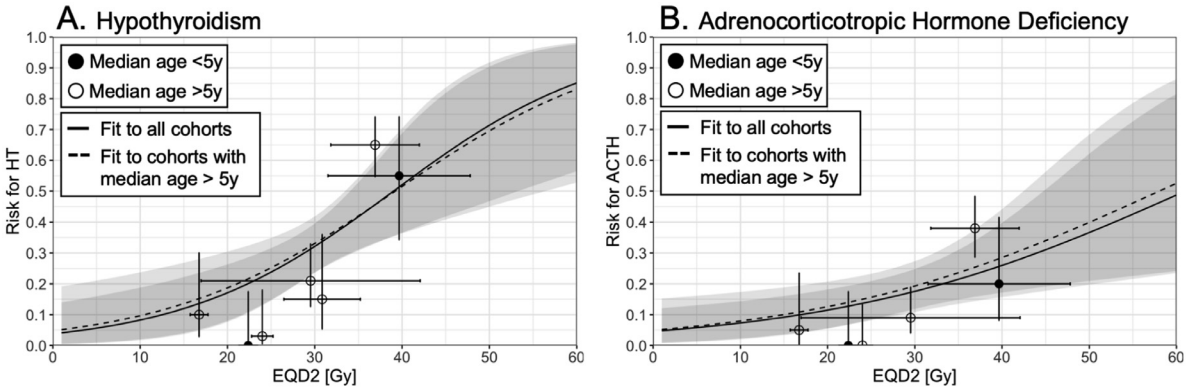

Fig. 3. Risk of HT (A) and ACTH deficiency (B) after radiation therapy to the hypothalamus/pituitary region described using a logistic model fitted to reported data in Table 1. Full line represents fit to all cohorts, and dotted line represents fit to only cohorts with median age >5 years (open symbols). HT best fit estimates: D_{50} = 39 Gy (34.1-53.2) and γ_{50} = 0.81 (0.46-1.35) for all cohorts; D_{50} = 39.2 Gy (33.5-56.3) and γ_{50} = 0.75 (0.37-1.4) for cohorts with >5-year median age. ACTH best fit estimates: D_{50} = 61 Gy (44.7-119.4) and γ_{50} = 0.76 (0.5-1.19) for all cohorts; D_{50} = 58 Gy (42.4-138.5) and γ_{50} = 0.74 (0.43-1.24) for cohorts with >5-year median age. Shaded area represents 95% CI of model fits. Each cohort in Table 1 is represented by a data point; the X error bars represent the total standard deviation (a convolution of the dose variance within the cohort with the estimated dosimetric uncertainty), and the Y error bars represent the binomial 95% CI. *Abbreviations:* ACTH = adrenocorticotropic hormone; EQD2 = equivalent dose with 2 Gy per fraction, using α/β ratio = 3; HT = central hypothyroidism.

Caveats

In many situations, RT is an important component of treatment for pediatric malignancies adjacent to or involving the HPA, and doses to these structures cannot be lowered while adequately treating the target. These data therefore provide information on likelihood of toxicity at a given dose of RT to the HPA and may be considered in treatment planning, though the balance between coverage of the target and dose to organs at risk must be carefully weighed for each clinical situation and discussed when counseling patients and families.

Limitations

This analysis has several limitations. The threshold for GHD varied between studies, and most studies did not provide quantitative data on growth hormone levels in patients at an individual level. As such, this analysis relied on the study definition of GHD and could not provide a quantitative analysis of the effect of RT on growth hormone values. In addition, methods of detecting hormone deficiencies also varied between studies, which could have potentially influenced the calculated number of affected patients and therefore the results. There was insufficient data in the literature to perform a meaningful analysis of other central endocrine outcomes of interest, including gonadotropin deficiency and metabolic syndrome, and the effect of RT on those outcomes could not be evaluated.

Although the removal of studies with median age <5 years led to an improved fit, it must be emphasized that the pooled data do not allow for firm conclusions about the effect of age on risk. These studies include significant fractions of very young children, so removing them eliminates the "noisiest" cohorts, which explains why the uncertainty is reduced and the steepness is increased while the D_{50} remains similar. Nevertheless, the limited data do suggest that the cohorts with lower median ages have greater risks than the overall group (ie, the majority of filled black symbols in Fig. 2A are above the full line that has been fitted to all of the cohorts), a trend that has been reported in several individual reports.[51,52]

While generous estimates of uncertainty were used for the estimated doses to the HPA across the individual studies (Table 1), a normal distribution of doses in the partial brain cohorts was assumed; if the actual distributions within these cohorts are skewed, this could in turn propagate to the estimated dose-response curve. This affects only the fits to all cohorts, but not the fits to only the whole brain RT studies in Fig. 2B and the estimates in Table 2. The dose to the hypothalamus and pituitary were assumed to be the same unless otherwise specified, which may have provided another potential source of error, particularly in cases involving partial brain irradiation, though we would expect any dose difference to be small. In addition, detailed dosimetric information was available in very few of the studies, which limited our ability to use many partial brain studies in our analysis and may have led to an overrepresentation of leukemia patients receiving whole brain RT in our cohort. The overrepresentation of leukemia patients in this cohort may reduce the generalizability of these results to patients in general who receive RT that may affect endocrine outcomes. Along these lines, patients in this cohort were treated for a range of diagnoses, and the other therapies they received as part of their overall treatment package may have also influenced endocrine outcomes. Best attempts were made to exclude patients for whom this was believed to be the case (eg, patients who underwent a known surgery that was

deemed likely to affect endocrine outcomes were excluded). Most patients in this analysis did not receive spinal RT, but there is the possibility of spinal field exit dose affecting adrenal or thyroid toxicity and potentially confounding HPA dose interpretation among the minority of patients who did receive spinal RT. In addition, this study included patients treated over an extended period of time, and it is likely that chemotherapeutic regimens and surgical techniques varied over that period.

Importantly, many studies did not include detailed pretreatment endocrine evaluation, and so the effect of RT itself on endocrine function could not always be determined. Further, follow-up intervals and number and type of tests performed to assess endocrine function were variable. Central endocrine function is affected by many factors, and even the effect of RT on endocrine outcomes appears to be modulated by factors such as patient age and length of follow-up.

Finally, some studies appeared to include overlapping patient cohorts, and best attempts were made to exclude articles that included the same patients in order to not overweight the outcomes of those particular individuals in our data set.

Data Reporting Standards

In future work, the following reporting standards are recommended to facilitate interpretation of data and allow for individual patient data pooling:

- Patient demographics, including age, sex/gender, and race
- Baseline medical conditions, including preexisting endocrine abnormalities
- Information on other disease-related therapies, including surgery and chemotherapy received
- Baseline endocrine evaluation before RT
- Age at time of RT and attained age at follow-up
- Full RT data, including dose, fractionation, RT technique, and dosimetric data including dose-volume histogram values for each individual endocrine organ at risk, including (where applicable) at least pituitary gland, hypothalamus, thyroid gland, testes (separately), and ovaries
- Use of National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 for endocrine outcomes, including hypopituitarism, hypothyroidism, and other endocrine disorders
- Endocrine evaluation after RT with quantitative results and time points

Future Investigations

Additional studies are needed to better understand and delineate the following:

- Dose-volume effects of RT on other central endocrine function outcomes, including LH, FSH, and the development of metabolic syndrome
- Effect of age at time of RT on GHD, HT, and ACTH deficiency
- Effect of length of follow-up on measured effect of RT on GHD, HT, and ACTH deficiency
- Effect of growth hormone replacement on linear growth and disease control outcomes
- Dose response for each lobe of the pituitary

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