Endocrine Deficiency As a Function of Radiation Dose to the Hypothalamus and Pituitary in Pediatric and Young Adult Patients With Brain Tumors

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Published at jco.org on August 17, 2018.

Clinical trial information: NCT00105560, NCT01063114, NCT01288235.

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0732-183X/18/3628w-2854w/\$20.00

ABSTRACT

Purpose

There are sparse data defining the dose response of radiation therapy (RT) to the hypothalamus and pituitary in pediatric and young adult patients with brain tumors. We examined the correlation between RT dose to these structures and development of endocrine dysfunction in this population.

Materials and Methods

Dosimetric and clinical data were collected from children and young adults (< 26 years of age) with brain tumors treated with proton RT on three prospective studies (2003 to 2016). Deficiencies of growth hormone (GH), thyroid hormone, adrenocorticotrophic hormone, and gonadotropins were determined clinically and serologically. Incidence of deficiency was estimated using the Kaplan-Meier method. Multivariate models were constructed accounting for radiation dose and age.

Results

Of 222 patients in the study, 189 were evaluable by actuarial analysis, with a median follow-up of 4.4 years (range, 0.1 to 13.3 years), with 31 patients (14%) excluded from actuarial analysis for having baseline hormone deficiency and two patients (0.9%) because of lack of follow-up. One hundred thirty patients (68.8%) with medulloblastoma were treated with craniospinal irradiation (CSI) and boost; most of the remaining patients (n = 56) received involved field RT, most commonly for ependymoma (13.8%; n = 26) and low-grade glioma (7.4%; n = 14). The 4-year actuarial rate of any hormone deficiency, growth hormone, thyroid hormone, adrenocorticotrophic hormone, and gonadotropin deficiencies were 48.8%, 37.4%, 20.5%, 6.9%, and 4.1%, respectively. Age at start of RT, time interval since treatment, and median dose to the combined hypothalamus and pituitary were correlated with increased incidence of deficiency.

Conclusion

Median hypothalamic and pituitary radiation dose, younger age, and longer follow-up time were associated with increased rates of endocrinopathy in children and young adults treated with radiotherapy for brain tumors.

J Clin Oncol 36:2854-2862. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Endocrine dysfunction is a common late effect experienced by children and adults with brain tumors treated with radiotherapy (RT) and is associated with significant morbidity and treatment cost for survivors.¹⁻³ Endocrinopathy results from injury to the hypothalamus and pituitary, with decreased production of growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), and gonadotropins (luteinizing hormone and follicle-stimulating

hormone). The largest cohort of long-term survivors of childhood brain tumors treated with chemotherapy and RT (with 27.3 years mean follow-up) demonstrates an estimated 40-year cumulative incidence of GH, thyrotropin, ACTH, and gonadotropin deficiency of 72.4%, 11.6%, 5.2%, and 24.4%, respectively.⁴ As long-term survival outcomes for these children improve, the late effects of treatment become increasingly important determinants of quality of life and medical expenditures.⁵

Cranial radiotherapy is a leading cause of hypothalamic and pituitary injury and hormone

ASSOCIATED CONTENT

Appendix
DOI: <https://doi.org/10.1200/JCO.2018.78.1492>

DOI: <https://doi.org/10.1200/JCO.2018.78.1492>

deficiency in children with brain tumors.^{6,7} GH deficiency after cranial radiotherapy is well documented in children with leukemia and brain tumors, with incidence correlated with radiation dose, ranging from 25% to 50% after 8 to 14.4 Gy total body irradiation,⁸ 0% to 66% after 18 to 24 Gy cranial RT,⁹⁻¹¹ and 80% to 90% after ≥ 30 Gy.^{7,12,13} Merchant et al¹⁴ modeled stimulated GH secretion as a function of hypothalamic radiation dose in pediatric patients with brain tumors, finding a 50% risk of impairment at 5 years after 16.1 Gy. Laughton et al¹⁵ found a 93% incidence of GH deficiency with no dose response in children with embryonal brain tumors treated with CSI and tumor-directed boost. This study also reported a dose-dependent difference in thyrotropin deficiency, with a 4-year cumulative incidence of 44% after ≥ 42 Gy versus 11% after < 42 Gy. However, there are no prospective quantitative data defining the radiation dose response of the hypothalamus and pituitary with respect to TSH, ACTH, and gonadotropin deficiency in children or adults.

Proton radiotherapy is used with increasing frequency for the treatment of children and young adults with brain tumors. Compared with photon RT, protons deliver less entrance dose and no exit dose. This reduces radiation exposure of normal intracranial structures, including the hypothalamus and pituitary, which should result in reduced toxic effects.¹⁶ Quantifying the radiation tolerance of the hypothalamus and pituitary is important for radiation treatment planning, because newer technologies using either proton or photon modalities can limit dose to critical structures.¹⁷⁻¹⁹ We present the first prospectively collected data, to our knowledge, relating hypothalamic and pituitary radiation dose with the development of endocrine deficiencies after proton treatment of brain tumors.

MATERIALS AND METHODS

Study Design and Participants

Dosimetric and clinical data were collected from pediatric and young adult patients (< 26 years of age) with brain tumors enrolled in two single-institutional and one multi-institutional prospective phase II clinical trials (2003 to 2016). Patients with embryonal neoplasms (eg, medulloblastoma) treated with CSI were enrolled in [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00105560) identifier: NCT00105560 (2003 to 2009) or [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01063114) identifier: NCT01063114 (2010 to 2016). Patients with brain tumors requiring focal RT were enrolled in [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01288235) identifier: NCT01288235 (2011 to 2015). The hypothalamus and pituitary were contoured on planning CT scans with MRI coregistration for generation of dose statistics. Studies were approved by our institutional review board, and patients or their parents/guardians provided written informed consent.

Treatment

Patients with medulloblastoma underwent resection followed by CSI and posterior fossa or tumor bed boost. All received chemotherapy, with the regimen determined by the patient's oncologist. Patients enrolled in NCT01288235 received tumor-directed proton RT with chemotherapy and surgery as clinically indicated. Passively scattered three-dimensional conformal proton RT was delivered in 1.8 Gy_{RBE} fractions, with dose prescribed in Gy_{RBE} using a relative biologic equivalent weighting of 1.1 Gy_{RBE}/Gy. Six patients received some photon treatment to avoid interruptions during cyclotron maintenance.

Outcome Variables and Assessments

The incidence of GH deficiency, hypothyroidism (primary and central), ACTH deficiency, and gonadotropin deficiency was the primary end point of this study and secondary end point of the prospective studies in which patients were enrolled. Evidence of endocrinopathy was based on clinical and biochemical diagnosis by an endocrinologist as documented in the medical record or at initiation of hormone replacement therapy. Diagnostic criteria for patients followed at the study institution are detailed in Appendix Table A1 (online only). Diagnostic criteria for patients followed at their home institution were at the discretion of the treating endocrinologist. All patients had a pretreatment endocrine

Table 1. Demographics and Treatment Details for All Patients and Those Who Met Inclusion Criteria for Survival Analysis With Follow-Up Data and Without Baseline Endocrinopathy

Demographic or Treatment	Total (N = 222)	Included in Analysis (n = 189)
Sex		
Male	121 (54.5)	102 (54.0)
Female	101 (45.5)	87 (46.0)
Race		
White	188 (84.7)	158 (83.6)
Other	34 (15.3)	31 (16.4)
Age at treatment, years	7.7 (1.1-25.9)	7.4 (1.1-25.9)
< 6	71 (32.0)	63 (33.3)
6-10	75 (33.8)	66 (34.9)
10-21	70 (31.5)	55 (29.1)
> 21	6 (2.7)	5 (2.6)
Histology		
Medulloblastoma	137 (61.7)	130 (68.8)
Ependymoma	28 (12.6)	26 (13.8)
Low-grade glioma	18 (8.1)	14 (7.4)
Craniopharyngioma	19 (8.6)	2 (1.1)
PNET/embryonal tumor	5 (2.3)	4 (2.1)
High-grade glioma	6 (2.7)	5 (2.6)
Meningioma	3 (1.4)	3 (1.6)
AT/RT	3 (1.4)	2 (1.1)
Other*	3 (1.4)	3 (1.6)
Site		
Supratentorial	54 (24.3)	30 (15.9)
Infratentorial	168 (75.7)	159 (84.1)
Year of RT	2012 (2003-2016)	2011 (2003-2016)
Follow-up, years	4.1 (0-13.3)	4.4 (0.12-13.3)
Extent of surgery		
GTR	133 (59.9)	124 (65.6)
NTR	22 (9.9)	19 (10.1)
STR	41 (18.5)	28 (14.8)
Biopsy only	10 (4.5)	9 (4.8)
Unknown	16 (7.2)	9 (4.8)
Extent of RT		
CSI plus boost	141 (63.5)	133 (70.4)
Involved field only	81 (36.5)	56 (29.6)
CSI dose, Gy_{RBE}	23.4 (18-36)	23.4 (18-36)
Hypothalamus dose, Gy_{RBE}	28.1 (0-54.6)	26.0 (0-54.6)
Pituitary dose, Gy_{RBE}	24.6 (0-57.3)	24.3 (0-57.3)
Progression of disease	33 (14.9)	29 (15.3)
Baseline hormone deficiency		
Any deficiency	31 (14.0)	0 (0)
Growth hormone	18 (8.1)	0 (0)
Thyroid	24 (10.8)	0 (0)
Cortisol	28 (12.6)	0 (0)
Sex hormone	13 (5.9)	0 (0)

NOTE. Data presented as No. (%) or median (range).

Abbreviations: AT/RT, atypical teratoid/rhabdoid tumor; CSI, craniospinal irradiation; GTR, gross total resection; NTR, near total resection; PNET, primitive neuroectodermal tumor; RBE, relative biological effectiveness; RT, radiation therapy; STR, subtotal resection.

*Other diagnoses with $n \leq 2$ included neurocytoma and pineoblastoma.

evaluation and were followed annually with physical examination; height and weight measurement; laboratory assessment, including TSH, free T₄, insulin-like growth factor (IGF)-1 with or without IGF binding protein (BP)-3, 8 AM cortisol, follicle-stimulating hormone, luteinizing hormone, and estradiol or testosterone levels (depending on sex); and bone age as assessed by wrist and hand radiograph.¹⁹ Patients who were unable to return for follow-up were followed remotely by requesting documentation of annual laboratory evaluations and clinical notes from patients and referring physicians. Patients with progressive disease were censored at date of disease progression.

Statistical Analysis

Incidence of hormone deficiency was estimated using the Kaplan-Meier method, with time calculated from start of radiation. Log-rank testing was performed to determine statistical significance of differences among stratified curves. Correlation between hypothalamic and pituitary dose was determined by least squares regression and Pearson's test. Parametric models of interval-censored survival data (stintreg package,

StataCorp, College Station, TX) with log-logistic (accelerated failure time) survival distribution were generated incorporating dose and age variables. For patients with deficiency, the interval was defined as time between diagnosis and prior follow-up. Proportionality of hazards for all end points was confirmed using the Schoenfeld residuals test (estat phtest in Stata) on a Cox model. Model goodness-of-fit was tested by confirming linearity of the Cox-Snell residuals plotted against the estimated cumulative hazard function corresponding to these residuals and by plotting model predictions superimposed on the cumulative incidence curves.

RESULTS

Of the 222 patients treated, 189 (54% male; 46% female) were evaluable by actuarial analysis, having a median follow-up of 4.4 years (range, 0.1 to 13.3 years). Of these, only seven patients had

Fig 1. (A) Cumulative incidence curve for the development of any hormone deficiency with 95% CIs. The model prediction is overlaid as a blue line. (B) Cumulative incidence curve for the development of any hormone deficiency stratified by hypothalamic dose ≤ 20 Gy_{RBE}, 20 to 40 Gy_{RBE}, and ≥ 40 Gy_{RBE}, with 95% CIs (shaded). The model prediction is overlaid as dashed lines. (C) Cumulative incidence curve for the development of any hormone deficiency stratified by age at time of treatment < 6 years old, 6 to 10 years old, and > 10 years old, with the model prediction overlaid as dashed lines.

< 1-year follow-up, and five had < 11 months of follow-up. Patients were excluded from actuarial endocrine analysis for baseline endocrinopathy (n = 31) and lack of follow-up (n = 2; Table 1). Of the 189 evaluable patients, medulloblastoma was the most common diagnosis in 130 of the patients (68.8%). Fifty-six patients (29.6%) with nonembryonal tumors received tumor-directed RT with diagnoses listed in Table 1. Complete laboratory values were available for the majority of patients at each follow-up as supplementation to clinical evaluation.

Baseline Hormone Deficiency

Of the 31 patients with baseline endocrinopathy at initiation of radiotherapy, 25 patients (80.6%) had suprasellar tumors. Of the 19 patients with craniopharyngioma, 89.5% had baseline deficiency. In contrast, baseline deficiency was rare among patients with medulloblastoma (3.7%; n = 5), ependymoma (7.1%; n = 2), and other posterior fossa tumors.

Incidence of Hormone Deficiency

Complete endocrine status was available at last follow-up for all patients. Actuarial rates of any hormone deficiency at 3, 4, and 5 years were 31.3%, 48.8%, and 55.5%, respectively (Fig 1A). GH deficiency was the commonest endocrinopathy (cumulative incidence, 33.3%), followed by hypothyroidism (20.1%, with 91% central TSH deficiency), ACTH (7.4%), and gonadotropins (4.2%), with actuarial rates at 3, 4, and 5 years reported in Tables 2 and 3. Of the three patients with primary thyroxine deficiency, all were compensated, and thyroid radiation dose was low (mean, 1.1 Gy_{RBE}; range, 0.6 to 1.7 Gy_{RBE}) and not different from patients without hypothyroidism (mean, 0.8 Gy_{RBE}; range, 0 to 7.1 Gy_{RBE}).

Radiation Dose and Endocrinopathy

Incidence of hormone deficiency was highest among patients who received a hypothalamic and pituitary median dose $\geq$ 40

Gy_{RBE} and lowest among those who received $\leq$ 20 Gy_{RBE} (Fig 1B). This dose dependence held for each hormone, with individual Kaplan-Meier curves depicted in Figure 2, and actuarial rates at 3, 4, and 5 years reported in Tables 2 and 3.

Selection of Dose Statistic

The close anatomic proximity of the hypothalamus and pituitary results in highly correlated dose profiles in each patient (slope = 0.860; adjusted R^2 = 0.686; Pearson correlation = 0.829; Appendix Fig 1A, online only). Given this correlation, analyses were performed using the mean of the median pituitary and hypothalamic doses. This composite dose statistic correlates closely with median dose for both the hypothalamus and pituitary (Figs A1B and A1C) and was validated by performing separate analyses using median pituitary and hypothalamic dose with indistinguishable results (data not shown).

Age and Endocrinopathy

When stratified by age, patients treated between 6 and 10 years of age had a higher rate of endocrinopathy than patients treated $\leq$ 6 years old. Patients $\geq$ 10 years of age at the time of treatment had the lowest incidence of hormone deficiency (Fig 1C). When looking at individual hormones, there was no significant difference among age groups in the rate of thyroxine, ACTH, or gonadotropin deficiency on the basis of log-rank testing. However, patients 6 to 10 years of age had a higher rate of GH deficiency than both younger and older patients (Fig 3).

Multivariate Analysis

Multivariate parametric models were constructed to estimate risk of endocrinopathy as a function of hypothalamic/pituitary dose and age at time of treatment (Fig 4 [graphical]; Appendix Table A2 and Equation, online only [model parameters]). For example, a 5-year-old who receives 20 Gy_{RBE} to the hypothalamus and pituitary has a 40% chance of developing endocrinopathy and a 30% chance of developing GH deficiency 5 years after treatment, whereas a 15-year-old who receives the same dose will have only a 23% chance of endocrinopathy at 5 years and < 5% chance of developing GH deficiency. This highlights the contribution of both dose and age in the development of endocrinopathy after cranial radiotherapy. Other factors, such as craniospinal radiation, chemotherapy, and extent of surgery, were

Table 2. Summary Table of Actuarial Rates of Hormone Deficiency Stratified by Age at Time of Treatment and Mean Hypothalamic and Pituitary Median Dose

Hormone Deficiency	3 Years (%)	4 Years (%)	5 Years (%)
Any hormone	31.3	48.8	55.5
GH	25.2	37.4	44.2
Thyroid hormone	11.9	20.5	25.8
ACTH	4.4	6.9	8.0
Gonadotropin	3.3	4.1	5.1
Any hormone deficiency by age group (years)			
< 6	25.6	46.8	53.5
6-10	45.4	60.2	71.9
> 10	22.9	39.8	42.4
Any hormone deficiency by mean hypothalamic and pituitary median dose, Gy _{RBE}			
< 20	4.2	9.0	9.0
20-40	28.5	46.7	55.5
> 40	60.4	83.5	86.8

Abbreviations: ACTH, adrenocorticotrophic hormone; GH, growth hormone; RBE, relative biological effectiveness.

Table 3. Summary Table of Actuarial Rates of Hormone Deficiency at 5 Years Stratified by Mean Hypothalamic and Pituitary Median Dose

Hormone Deficiency	$\leq$ 20 Gy _{RBE}	20-40 Gy _{RBE}	$\geq$ 40 Gy _{RBE}
GH	9.0	39.6	78.8
Thyroid hormone	4.2	24.5	42.8
ACTH	4.2	4.2	18.2
Gonadotropin	0	2.9	14.0

NOTE. Data presented as %.

Abbreviations: ACTH, adrenocorticotrophic hormone; GH, growth hormone; RBE, relative biological effectiveness.

Fig 2. Cumulative incidence of hormone deficiency stratified by mean D50 (median dose) for the hypothalamus and pituitary for (A) growth hormone (GH), (B) thyroid hormone, (C) adrenocorticotropic hormone (ACTH), or (D) gonadotropin.

examined and did not contribute significantly to the risk of endocrinopathy.

DISCUSSION

We present the first study modeling the effect of hypothalamic and pituitary radiation dose on endocrine outcomes in pediatric and young adult patients with brain tumors treated with proton radiotherapy. This is the largest study of this kind, providing a quantitative relationship between hypothalamic and pituitary radiation dose and deficiencies of GH, thyroxine, ACTH, and gonadotropins on the basis of prospectively collected data. In addition to radiation dose, other independent predictors of

endocrinopathy were follow-up time and age at treatment. These factors were combined to produce a clinically relevant model for estimating the risk of developing endocrinopathy after radiotherapy for brain tumors in children and young adults.

Many patients had hormone deficiencies before RT (14%), primarily driven by tumor location and histology. Most patients with suprasellar tumors involving or abutting the hypothalamus and pituitary had baseline deficiencies (80.6%). In contrast, only 3.7% of patients with medulloblastoma and 4.2% of patients with nonembryonal infratentorial tumors had baseline hormone deficiencies. This incidence is below the previously reported pre-RT incidence of both GH deficiency (23% to 38%) and any deficiency (up to 66%).^{14,20} The discrepancy may be partially explained by

Fig 3. Cumulative incidence of hormone deficiency stratified by age at time of radiation treatment of (A) growth hormone (GH), (B) thyroid hormone, (C) adrenocorticotropic hormone (ACTH), or (D) gonadotropin.

a higher proportion of infratentorial tumors and by different screening methodologies. These data highlight the importance of screening for endocrine dysfunction in patients before cranial radiation, especially those with supratentorial tumors.

We observed a clear dose response to all hormones tested, with GH deficiency being the most sensitive to radiation. At doses ≤ 20 Gy_{RBE}, there was only a 9% actuarial incidence at 5 years compared with 40% after 20 to 40 Gy_{RBE} and 79% after ≥ 40 Gy_{RBE}. This is comparable to prior studies; Rappaport et al²¹ found no deficiency at 4 years after 18 Gy cranial RT, 56% after 24 Gy, and 75% after 45 Gy.²¹⁻²³ However, this differs from the 94% incidence of GH deficiency without dose response in children with embryonal tumors treated with 26 to 58 Gy (including CSI) reported by Laughton et al.¹⁵ In contrast, only 58% of patients with embryonal

tumors in our study developed clinical GH deficiency, and this was dose dependent. The discrepancy is partially explained by inclusion of patients who received lower hypothalamic dose (≥ 26 Gy v 0 to 54.6 Gy in this study), differences in diagnostic methods (GH stimulation testing for all patients v testing only when clinically indicated), and differences in threshold indicative of deficiency on the basis of peak GH after stimulation testing continues to be debated.²⁴

Merchant et al¹⁴ published a comprehensive study modeling GH secretion as a function of hypothalamic dose in children with nonembryonal brain tumors treated with photon radiotherapy. With a median follow-up of 3 years, they reported a tolerated dose (TD)_{50/5} of 16.1 Gy to the hypothalamus (the dose associated with 50% probability of developing decreased GH secretion at 5 years).

Fig 4. Models relating mean D50 (median dose) to the hypothalamus and pituitary with risk for hormone deficiency at 5 years, stratified by age at time of radiotherapy (RT) for (A) any hormone, (B) growth hormone (GH), (C) thyroid hormone, (D) adrenocorticotrophic hormone (ACTH), and (E) gonadotropin. Solid lines represent the model prediction and dashed lines represent the 95% CIs for select groups.

This is in comparison with an age-dependent $TD_{50/5}$ for developing GH deficiency ranging from 25 to 50 Gy_{RBE} from our model. The difference between our results likely stems from the different study end points. Merchant et al¹⁴ performed arginine-levodopa stimulation testing in all patients to assess GH secretion. Our study end point was clinical GH deficiency, and because the peak GH response on provocative testing is affected by factors such as body weight, the stimulating agent(s) used, and priming with sex steroids before testing leading to suboptimal post-test probability,²⁴⁻²⁷

we chose to perform provocative testing only for patients with clinical suspicion of GH deficiency, namely those with reduced growth rate in the context of pubertal (Tanner) staging, laboratory values (low IGF-1 $\pm$ IGFBP-3), and delay in bone age (in those whose epiphyses were still open).

Hypothyroidism (mostly TSH deficiency) was the second most common endocrinopathy in our patients, with a 5-year actuarial rate of 4.2%, 24.5%, and 42.8% after hypothalamic and pituitary doses of ≤ 20 Gy_{RBE}, 20 to 40 Gy_{RBE}, and ≥ 40 Gy_{RBE},

respectively. This is concordant with prior studies.^{12,15,28} However, the cumulative incidence of primary hypothyroidism (3% after CSI and 1.6% overall) is substantially lower than previous reports of 56% to 65% incidence after CSI.^{15,29,30} This is likely due to differences between proton and photon CSI. In contrast to medulloblastoma treated with photon CSI, with protons there is little thyroid exposure from spinal field exit dose. Therefore, the predominant thyroid hormone deficiency seen in our study was a central TSH deficiency. This is supported by Eaton et al,³¹ who have demonstrated lower rates of thyroid hormone deficiency in proton- versus photon-treated cohorts of children with standard-risk medulloblastoma.

The incidence of ACTH deficiency was infrequent in our study, with a 5-year actuarial rate of 8%, occurring almost exclusively after ≥ 40 Gy_{RBE} to the hypothalamus and pituitary. Although lower than some studies,¹⁵ this is concordant with most prior studies reporting deficiency only after doses > 40 to 50 Gy.^{12,32-34} Similarly, gonadotropin deficiency was relatively rare, with a 5-year incidence of 5.1%, occurring almost exclusively after ≥ 40 Gy_{RBE}. This is also comparable to prior studies with similar follow-up.³⁵⁻³⁷

Although the median follow-up time in this study of 4.4 years is comparable to or longer than that of other studies, it may result in underestimation of endocrinopathy developed later in life. The median follow-up may also affect the models that assume the time dependence of the relative risk of endocrinopathy is proportional at any age of radiation exposure. Although a useful assumption that withstood statistical testing, patients are more likely to be diagnosed with gonadotropin deficiencies in or around puberty compared with earlier ages.³⁸ Another potential limitation is that hormonal contraception use by young women may mask the development of gonadotropin deficiency, leading to a slight underestimate of deficiency. To this point, of the 39 female patients > 15 years old at last follow-up at risk for gonadotropin deficiency, 28% received hormonal contraception. An opposite age effect may underestimate GH deficiency in older patients, because GH deficiency is most likely diagnosed before epiphyseal fusion (ie, during childhood and adolescence), rather than after growth is complete. Although low IGF-1 $\pm$ IGFBP-3 levels would typically signal the possibility of adult GH deficiency, adult patients were less likely to have annual testing in the absence of clinical symptoms of deficiency. With many years of additional follow-up, the validity of these models and underlying assumptions will become clearer.

The end point of clinical diagnosis of endocrinopathy rather than specific laboratory values could be seen as a study limitation. This end point was chosen for its clinical relevance and by practical necessity, because many study patients traveled for proton therapy and received endocrine follow-up at their home institution. This may detract from the precision of the endocrine outcomes but does not affect the accuracy. Annual follow-up with an endocrinologist was confirmed by a central study team, and standard diagnostic criteria were used for determining endocrinopathy (outlined in Appendix Table A1); however, the exact laboratory cutoffs were left to the discretion of the treating endocrinologist. In rare cases when information specifically confirming the presence or absence of deficiency was not available, this time point was not counted as

follow-up to avoid underestimating the incidence of deficiency due to under-reporting in the documentation.

Another limitation of this methodology is the difficulty in discerning between central and primary hormone deficiency for diagnoses made at outside institutions. However, the risk for primary endocrine deficiency is low in this population,³⁹ and central deficiency was confirmed for the 60% of diagnoses made at the study institutions, with the only exception being three patients treated with CSI who had compensated primary hypothyroidism despite low-dose thyroid exposure (< 2 Gy). In these patients, other causes may mediate primary thyroid deficiency.

The relationship between hypothalamic and pituitary dose and endocrine deficiency reported here has important implications for treatment. Modern radiotherapy techniques using proton or intensity-modulated photon radiotherapy allow for the identification and avoidance of the hypothalamus and pituitary, which should decrease the risk of endocrinopathy. This supports the continued use of proton RT or IMRT for pediatric brain tumors. Another important finding is that the dose-response relationship is age dependent, and therefore data from adult patients are not appropriately applied to the pediatric and young adult population.

In summary, we present models for predicting risk of GH, thyroid hormone, cortisol, and sex steroid deficiency on the basis of patient age at treatment and radiation dose to the hypothalamus and pituitary in children and young adults with brain tumors treated with radiotherapy. These data provide justification for minimizing the dose to the pituitary and hypothalamus when possible using modern radiotherapy techniques. The models presented here will be a useful clinical tool that can be used to predict the risk of endocrinopathy after radiotherapy for brain tumors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Prior Presentation

Presented at the annual meeting of the American Society of Radiation Oncology, Boston, MA, September 25-28, 2016.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Endocrine Deficiency As a Function of Radiation Dose to the Hypothalamus and Pituitary in Pediatric and Young Adult Patients With Brain Tumors

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Ralph E. Vatner

Honoraria: Varian Medical Systems

Research Funding: Varian Medical Systems (Inst)

Andrzej Niemierko

No relationship to disclose

Madhusmita Misra

Consulting or Advisory Role: Novo Nordisk, Sanofi

Research Funding: Novo Nordisk

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No relationship to disclose

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No relationship to disclose

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No relationship to disclose

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No relationship to disclose

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No relationship to disclose

Arnold C. Paulino

Employment: MD Anderson Cancer Center

Patents, Royalties, Other Intellectual Property: Royalty from Elsevier for book on positron emission tomography/computed tomography in radiotherapy treatment planning

Travel, Accommodations, Expenses: Henry Ford Hospital

Takara Stanley

Consulting or Advisory Role: TheraTech

Research Funding: Novo Nordisk, Kowa

Shannon M. MacDonald

No relationship to disclose

Nancy J. Tarbell

No relationship to disclose

Torunn I. Yock

Research Funding: IBA, Protom, Elekta

Appendix

Equation A1

To fit our interval-censored data, we used the stintreg package (StataCorp, College Station, TX) using a parametric survival distribution to model cumulative incidence of hormone deficiency. Specifically, we used a log-logistic distribution (accelerated failure time metric) of the form:

$$\frac{1}{1 + (\lambda_i t_i)^{\frac{1}{\gamma}}} \quad \text{where} \quad \lambda_i = \exp(-x_i \beta)$$

and γ is an ancillary parameter. The best-fit model parameter estimates for all investigated end points are listed in [Table A2](#). Our independent variables are age, age², and dose (average of median hypothalamic and median pituitary dose). Therefore:

$$\lambda_i = \exp\left(-\left(\text{const} + \beta_{\text{age}} \text{age}_i + \beta_{\text{age}^2} \text{age}_i^2 + \beta_{\text{dose}} \text{dose}\right)\right)$$

Fig A1. (A) Plot of median hypothalamic dose versus median pituitary dose for each patient showing the correlation between doses to the two structures. (B) Plot of mean D50 (median dose) for hypothalamus and pituitary versus median hypothalamic dose, and (C) median pituitary dose for each patient showing the correlation between dose to the composite variable and these two structures. Development of any hormone deficiency is noted by gold triangles, and no deficiency is noted by blue circles. The gray line represents a perfect 1:1 correlation, and the blue line represents the least squares linear regression.

Table A1. Diagnostic Criteria for Endocrinopathy

Hormone Deficiency	Criteria
GH deficiency	GH stimulation testing was recommended for patients with clinical suspicion of GH deficiency on the basis of a combination of reduced growth rate (in the context of pubertal Tanner stage), low IGF-1 $\pm$ IGFBP-3 (for pubertal stage), and delayed bone age in those with open epiphyses. In those with closed epiphyses, low IGF-1 $\pm$ IGFBP-3 for age prompted GH stimulation testing. The diagnostic threshold values for GH deficiency on the basis of the peak GH response after GH stimulation testing was at the discretion of the treating endocrinologists, but always < 10 ng/mL.
Thyroid deficiency	A normal or low TSH with a free T4 below the lower limit of normal was considered indicative of TSH deficiency, whereas an elevated TSH with a normal or low free T4 indicated primary hypothyroidism.
ACTH deficiency	Patients with morning cortisol levels between 3 and 10 μ g/dL were evaluated with a high-dose ACTH stimulation test. An 8 AM cortisol of < 3 μ g/dL or a peak stimulated cortisol of < 18 μ g/dL with a nonelevated ACTH was considered indicative of ACTH deficiency. An unstimulated cortisol ≥ 10 μ g/dL or a peak stimulated cortisol of ≥ 18 μ g/dL was considered normal.
Gonadotropin deficiency	In females, absence of any secondary sexual characteristics at 13 years, absence of menarche at 15 years, or secondary amenorrhea with low estradiol levels and nonelevated gonadotropin levels was considered evidence of hypogonadotropic hypogonadism. In males, low morning testosterone and nonelevated gonadotropin levels after 14 years of age were considered evidence of hypogonadotropic hypogonadism. Clinical symptoms of hypogonadism were elicited in pubertal and postpubertal male patients. It can be difficult to differentiate hypogonadotropic hypogonadism from constitutional delay in growth and puberty. Where necessary, DHEAS levels and follow-up clinical and biochemical data were used to differentiate the two conditions.

Abbreviations: ACTH, adrenocorticotrophic hormone; DHEAS, dehydroepiandrosterone; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; RBE, relative biological effectiveness; TSH, thyroid-stimulating hormone.

Table A2. Multivariate Model Parameters

Deficiency	Covariate	Coefficient (95% CI)	P
Any	Dose*	-0.049 (-0.065 to -0.033)	< .0005
	Age	-0.106 (-0.267 to 0.056)	.2
	Age ²	0.007 (-0.001 to 0.015)	.05
	Constant	3.13 (2.29 to -3.98)	< .0005
	γ	0.56 (0.46 to 0.67)	< .0005
GH	Dose*	-0.054 (-0.073 to -0.036)	< .0005
	Age	-0.346 (-.610 to -0.082)	.01
	Age ²	0.024 (0.009 to 0.039)	.001
	Constant	4.26 (3.05 to 5.50)	< .0005
	γ	0.55 (0.44 to 0.68)	< .0005
ACTH	Dose*	-0.77 (-0.136 to -0.018)	.01
	Age	-0.45 (-1.07 to 0.17)	.1
	Age ²	0.019 (-0.082 to 0.047)	.2
	Constant	8.68 (4.15 to 13.2)	< .0005
	γ	0.91 (0.57 to 1.46)	< .0005
Thyroid	Dose*	-0.053 (-0.083 to -0.024)	< .0005
	Age	-0.13 (-0.43 to 0.16)	.4
	Age ²	0.008 (-0.005 to 0.32)	.2
	Constant	4.69 (2.96 to 6.42)	< .0005
	γ	0.80 (0.61 to 1.06)	< .0005
Gonadotropin	Dose*	-0.09 (-0.17 to -0.009)	.03
	Age	-0.73 (-1.7 to 0.23)	.1
	Age ²	0.027 (-0.012 to 0.066)	.2
	Constant	11.7 (3.96 to 19.4)	< .0005
	γ	0.87 (0.48 to 1.57)	< .0005

Abbreviations: ACTH, adrenocorticotrophic hormone; GH, growth hormone.

*Dose covariate is equal to the mean of the median doses for the pituitary and hypothalamus volumes.