Neuro-Oncology

Neuro-Oncology 18(6), 881–887, 2016
doi:10.1093/neuonc/nov302
Advance Access date 19 December 2015

Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma

Bree R. Eaton, Natia Esiashvili, Sungjin Kim, Briana Patterson, Elizabeth A. Weyman, Lauren T. Thornton, Claire Mazewski, Tobey J. MacDonald, David Ebb, Shannon M. MacDonald, Nancy J. Tarbell, and Torunn I. Yock

Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia (B.R.E., N.E.); Pediatrics, Emory University School of Medicine and Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta, Atlanta, Georgia (B.P., C.M., T.J.M.); Biostatistics and Bioinformatics Research Center, Cedars-Sinai Medical Center, Los Angeles, California (S.K.); Pediatrics, Massachusetts General Hospital, Boston, Massachusetts (D.E.); Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts (B.R.E., E.A.W., L.T.T., S.M.M., N.J.T., T.I.Y.)

Corresponding Author: Torunn I Yock, MD, MCH, Massachusetts General Hospital, 55 Fruit Street, Proton Center, Room 110, Boston, MA 02114 (tyock@partners.org).

Background. Endocrine dysfunction is a common sequela of craniospinal irradiation (CSI). Dosimetric data suggest that proton radiotherapy (PRT) may reduce radiation-associated endocrine dysfunction but clinical data are limited.

Methods. Seventy-seven children were treated with chemotherapy and proton ($n = 40$) or photon ($n = 37$) radiation between 2000 and 2009 with $\geq$3 years of endocrine screening. The incidence of multiple endocrinopathies among the proton and photon cohorts is compared. Multivariable analysis and propensity score adjusted analysis are performed to estimate the effect of radiotherapy type while adjusting for other variables.

Results. The median age at diagnosis was 6.2 and 8.3 years for the proton and photon cohorts, respectively ($P = .010$). Cohorts were similar with respect to gender, histology, CSI dose, and total radiotherapy dose and whether the radiotherapy boost was delivered to the posterior fossa or tumor bed. The median follow-up time was 5.8 years for proton patients and 7.0 years for photon patients ($P = .010$). PRT was associated with a reduced risk of hypothyroidism (23% vs 69%, $P < .001$), sex hormone deficiency (3% vs 19%, $P = .025$), requirement for any endocrine replacement therapy (55% vs 78%, $P = .030$), and a greater height standard deviation score (mean ($\pm$ SD) -1.19 ($\pm$ 1.22) vs -2 ($\pm$ 1.35), $P = .020$) on both univariate and multivariate and propensity score adjusted analysis. There was no significant difference in the incidence of growth hormone deficiency (53% vs 57%), adrenal insufficiency (5% vs 8%), or precocious puberty (18% vs 16%).

Conclusions. Proton radiotherapy may reduce the risk of some, but not all, radiation-associated late endocrine abnormalities.

Keywords: endocrine, medulloblastoma, proton, photon, radiotherapy.

Endocrine dysfunction is a well-recognized treatment-related sequela of cranial irradiation in children.[1,2] Children receiving craniospinal irradiation (CSI) for medulloblastoma are at risk for multiple endocrinopathies, including growth hormone deficiency (GHD), hypothyroidism, adrenal insufficiency, and abnormal sex hormone production manifested as either hypogonadism or precocious puberty.[3] These long-term deficiencies are a significant cause of morbidity among brain tumor survivors, occurring in up to 80% of the population, and are associated with an increased risk of multiple other medical problems and a need for chronic management, with a high cost of medical care.[3,4]

While endocrine dysfunction following cranial radiotherapy for brain tumor patients is most commonly central in origin and directly related to hypothalamic pituitary axis (HPA) injury, primary gonadal or thyroid function may also be impacted in the setting of CSI and/or chemotherapy.[5–10] The risk of endocrine dysfunction is well recognized to be directly related to the dose of radiation received to the HPA, thyroid, or gonads.[8–11] In multiple dosimetric comparison studies for pediatric medulloblastoma, the use of proton radiotherapy (PRT) has demonstrated the ability to reduce the radiation dose received to the HPA and results in near complete avoidance of the thyroid and gonads compared with either 3D or intensity-modulated

Received 8 July 2015; accepted 3 November 2015

photon therapy.[12–14] Modeling estimates based on this dosimetric benefit have estimated proton therapy to be associated with a reduced risk of late endocrine effects when compared with photon therapy.[15]

Despite the dosimetric advantage of proton therapy, clinical data comparing long-term endocrine dysfunction with the use of proton and photon therapy are needed. The purpose of this study is to compare long-term incidence of multiple endocrinopathies among matched cohorts of patients treated with either PRT or photon radiotherapy (XRT) for standard risk medulloblastoma.

Materials and Methods

Patient Selection

This multi-institutional cohort study includes children with standard risk medulloblastoma treated with PRT at Massachusetts General Hospital or XRT at Emory University between 2000 and 2009. Standard risk patients met the following criteria for inclusion: age >3 years at diagnosis, <1.5 cm^2 residual disease after surgery, and M0 disease based on MRI of the brain and spine and cerebrospinal fluid cytology examination. Only patients with ≥3 years of follow-up with routine endocrine screening and without disease progression or receipt of salvage therapy were included for late endocrine effects analysis. Patients treated at Massachusetts General Hospital were prospectively enrolled in the phase II study NCT00105560.[16] Concurrent enrollment in Children's Oncology Group or other protocols was allowed. Institutional review board approval at both institutions was obtained for this analysis.

Treatment

All patients underwent maximal safe resection of the primary tumor followed by CSI and RT involved field (IF) or posterior fossa (PF) boost and chemotherapy consisting of vincristine, cisplatin, cyclophosphamide, and/or lomustine. Patients underwent either prone and/or supine CT simulation for RT planning. The CSI target volume included the entire subarachnoid volume and nerve roots for all patients. The whole vertebral body was also included in skeletally immature patients. PRT was delivered with 3D conformal (3DC) PRT, and dose was prescribed in grays using the relative biological equivalent value of 1.1. XRT was delivered with either 3DC XRT or intensity-modulated radiation therapy (IMRT).[17] CSI dose range was 18–27 Gy. All patients received 1.8 Gy per fraction to a cumulative dose of 54–55.8 Gy following IF or PF boost, with the exception of one XRT patient who was treated with 1.2 Gy per fraction twice daily to a cumulative total dose of 60 Gy.

Outcome Variables and Assessments

The primary endpoints for this study were the incidence of hypothyroidism, GHD, adrenal insufficiency, sex hormone deficiency, precocious puberty, the need for any endocrine replacement therapy, and height and body mass index (BMI) standard deviation score (SDS) at last follow-up. Patients were considered to have any of the endocrinopathy outcomes listed above when the clinical diagnosis was made and documented in the medical record by the endocrinologist or treating oncologist or when medical management for the endocrinopathy was initiated.

After completion of radiotherapy, patients underwent routine endocrine screening, including physical exam, height and weight measurement, and laboratory assessment every 6 months to 1 year with either an endocrinologist or an oncologist according to Children's Oncology Group guidelines. Laboratory assessment included thyroid stimulating hormone, free T4, insulin-like growth factor (IGF)−1 ± IGF binding protein−3, estrogen, testosterone, follicle stimulating hormone, luteinizing hormone (LH), and 8 AM cortisol. Patients with abnormal morning cortisol levels were evaluated with dynamic adrenal function testing. Growth hormone (GH) stimulation testing was recommended for patients with a clinical suspicion of GHD based on growth rate and/or IGF-1 levels. Institutional practice among the photon cohort limited the use of GH stimulation testing to only those patients/families who agreed to receive GH replacement therapy should their testing document GHD. Patients/families who indicated that they would not accept GH treatment were not tested. Onset of puberty was defined in males by enlargement of the phallus and development of pubic hair associated with elevation of LH and testosterone. In females, onset of puberty was defined by Tanner staging of the breast. Precocious puberty was defined as puberty at an abnormally early age (<8 y old for girls and 9 y old for boys). Sex steroid deficiency was defined as a clinically significant lack of production of sex steroids, requiring exogenous replacement of these hormones. Height and BMI SDS were calculated by taking into account gender and age for patients up to age 18.[18]

Statistical Analysis

Patients' characteristics were summarized and compared between those treated with PRT and those treated with XRT by Wilcoxon rank sum test for numerical covariates and chi-square test or Fisher's exact test for categorical covariates, where appropriate. Covariates included patient age, gender, histology, whether surgery was gross total resection or <1.5 cm^2 residual remained, year of diagnosis, CSI dose, total RT dose, and whether RT boost was IF or whole PF. Univariate association of each categorical endocrine outcome variable with covariates was examined with the Wilcoxon rank sum test for numerical covariates and the chi-square test or Fischer's exact test for categorical covariates, where appropriate. Multivariable analysis was conducted by entering all covariates into a logistic regression model and using a backward variable selection method with an alpha level of 0.2 removal criteria unless otherwise stated. For height and BMI SDS, we used an ANOVA or Spearman rank correlation coefficient for univariate analysis, where appropriate. Multivariable analysis was carried out by entering all covariates into a general linear model and using a backward selection method with an alpha level of 0.2 for removal criteria. For all multivariable analyses, RT type was forced in the model and the models were stratified by diagnosis year. Follow-up time was calculated from completion of RT until last date of follow-up.

A propensity score analysis was further performed to balance potential confounding factors between the 2 RT types. A multivariable logistic regression model was employed to predict RT type (PRT vs XRT) after adjusting for gender, date of

diagnosis, histology, location of RT boost, age at diagnosis, and RT CSI dose. An estimated propensity score, which is the predicted probability of receiving PRT, was assigned to each patient. To adjust for any patient differences between the 2 RT types, propensity score analysis was performed in 3 ways: (i) propensity score as a predictor was included in the multivariable model; (ii) propensity score was used to create weights, the inverse probability of treatment weighting; and (iii) propensity score matching, in which patients treated with PRT were matched in a 1:1 ratio to those treated with XRT according to gender, age, date of diagnosis, histology, location of RT boost, and RT CSI dose, using a greedy algorithm with the nearest available pair matching method on estimated propensity score.[19–21] Whether or not the propensity score adjusted models had been adequately specified was examined by comparing covariates between patients treated with PRT or XRT by a logistic regression model for categorical covariates and a general linear model for numerical covariates.[22] All analyses were done using SAS 9.3, with a significance level of .05.

Results

Patient Population

Eighty-eight patients were treated with PRT or XRT for standard risk medulloblastoma between 2000 and 2009. Ten patients were ineligible due to early recurrent disease or death within 3 years of diagnosis and one patient was ineligible due to lack of available endocrine follow-up data, leaving 77 patients who met eligibility criteria for inclusion in the late endocrine effects analysis (Table 1). Cohorts were similar with respect to gender, histology, presence of residual disease after surgery, CSI dose, total RT dose, and whether the RT boost was delivered to the PF or tumor bed. Patients treated with PRT were more likely to have received their diagnoses in 2005–2009 (80% vs 51%) and were younger than those treated with XRT (median age, 6.2 vs 8.3 y). Among the photon cohort, boost treatment was delivered with 3DC RT in 13 patients (35%) and IMRT in 24 patients (65%).

Table 1. Patient characteristics among the proton- and photon-treated cohorts

Covariate	RT Type		*P*
	Proton Therapy ($N = 40$)	Photon Therapy ($N = 37$)	
Age, y, at diagnosis, median (range)	6.2 (3.3–21.9)	8.3 (3.4–19.5)	.010
Gender, *n* (%)			
Female	19 (47.5)	13 (35.1)	.271
Male	21 (52.5)	24 (64.9)	
Date of diagnosis, *n* (%)			
2000–2004	8 (20)	18 (48.6)	.008
2005–2009	32 (80)	19 (51.4)	
Histology, *n* (%)			
Classic	31 (77.5)	32 (86.5)	.625
Anaplastic/large cell	4 (10)	2 (5.4)	
Other	5 (12.5)	3 (8.1)	
Residual disease after surgery, *n* (%)			
<1.5 cm^2	5 (12.5)	1 (2.7)	.202
None/gross total resection	35 (87.5)	36 (97.3)	
Location of RT boost, *n* (%)			
Tumor bed (TB)	24 (60)	18 (51.4)	.615
Posterior fossa (PF)	12 (30)	11 (31.4)	
PF → TB[a]	4 (10)	6 (17.2)	
CSI dose, Gy, median (range)	23.4 (18–27)	23.4 (18–26.4)	.681
Total dose to primary, *n* (%)			
54–55.8 Gy	40 (100)	36 (97.3)	.481
>55.8 Gy	0 (0)	1 (2.7)	
Days from surgery to RT start, median (range)	31 (24–219)	29 (11–60)	.574
Months RT duration, median (range)	1.42 (1.29–1.55)	1.39 (0.89–2.71)	.456

P-value is calculated by Wilcoxon rank sum test for numerical covariates and by chi-square test or Fisher's exact test for categorical covariates, where appropriate.
[a]Indicates boost to posterior fossa followed by a cone-down to the tumor bed only.

Endocrine Outcomes

The median (range) follow-up time was 7.0 years (3.5–13.5) for the photon cohort and 5.8 years (3.4–9.9) for the proton cohort ($P = .010$). The incidence of each endocrine outcome according to RT type and other covariates is listed in Table 2 for categorical outcomes and Table 3 for height and weight SDS. There was a statistically significant lower incidence of hypothyroidism (23% vs 69%, $P < .001$), sex hormone deficiency (3% vs 19%, $P = .025$), and need for any endocrine replacement therapy (55% vs 78%, $P = .030$), as well as a significantly greater mean height SDS at last follow-up (-1.19 vs -2.0, $P = .020$) among patients treated with PRT compared with patients treated with XRT. All significant associations found between endocrine outcome variables and covariates on univariate analysis are listed in Tables 2 and 3. Among the patients with a diagnosis of GHD, 18 of 21 patients (85.7%) in the proton cohort and 16 of 21 patients (76.2%) in the photon cohort received GH replacement ($P = .697$).

On multivariable analysis (Table 4), after taking into account other prognostic variables, PRT remained associated with a reduced risk of hypothyroidism (odds ratio [OR], 0.13; 95% CI, 0.04–0.41; $P < .001$), sex hormone deficiency (OR, 0.06; 95% CI, 0.01–0.55; $P = .013$), need for endocrine replacement therapy (OR, 0.30; 95% CI, 0.09–0.99; $P = .047$), and greater height SDS at last follow-up (parameter estimate, 0.89; 95% CI, 0.24–1.54; $P = .008$). Other significant associations on multivariable analysis existed between hypothyroidism and higher CSI dose, between GHD and male gender, classic histology, and younger age, and between the need for endocrine replacement therapy and classic histology (Table 4). A trend also existed between the need for endocrine replacement therapy and male gender.

Propensity Score Analysis

No significant differences in covariates between the PRT and XRT cohorts existed in any of the 3 propensity-score adjusted

Table 2. Univariate analysis of endocrine dysfunction

Outcome	Covariate	Yes	No	*P*
Hypothyroidism	PRT	9 (22.5)	31 (77.5)	<.001
	XRT	24 (64.9)	13 (35.1)	
	CSI dose	23.4 (23.4–26.4)	23.4 (18–27)	.031
	Primary dose[a]	54 (54–60)	54 (54–55.8)	.037
Growth hormone deficiency	PRT	21 (52.5)	19 (47.5)	.708
	XRT	21 (56.76)	16 (43.24)	
	Male	30 (66.7)	15 (33.3)	.011
	Female	12 (37.5)	20 (62.5)	
	Classic histology	38 (60.3)	25 (39.7)	.031
	Other histologies[b]	4 (28.6)	10 (71.4)	
Adrenal insufficiency	PRT	2 (5)	38 (95)	.667
	XRT	3 (8.11)	34 (91.89)	
	Age	12 (9.1–20)	6.9 (3.3–21.9)	.007
	CSI dose	23.4 (23.4–27)	23.4 (18–26.4)	.078
Sex hormone deficiency	PRT	1 (2.5)	39 (97.5)	.025
	XRT	7 (18.92)	30 (81.08)	
	Age	10.1 (8–16.2)	6.8 (3.3–21.9)	.014
Precocious puberty	PRT	7 (17.5)	33 (82.5)	.881
	XRT	6 (16.22)	31 (83.78)	
	2000–2004[c]	9 (34.62)	17 (65.38)	.007
	2005–2009	4 (7.84)	47 (92.16)	
Endocrine replacement therapy	PRT	22 (55)	18 (45)	.030
	XRT	29 (78.38)	8 (21.62)	
	Male	34 (75.56)	11 (24.44)	.040
	Female	17 (53.13)	15 (46.88)	
	Classic histology	45 (71.43)	18 (28.57)	.060
	Others[b]	6 (42.86)	8 (57.14)	

RT type and other covariates with $P \leq .10$ are presented. Data are presented as *n* (%) or median (range).
P-value is calculated by Wilcoxon rank sum test for numerical covariates and by chi-square test or Fisher's exact test for categorical covariates, where appropriate.
[a]As continuous.
[b]Includes anaplastic/large cell/other.
[c]Represents year of diagnosis.

Table 3. Univariate analysis of height and BMI SDS

Outcome	Covariate	*N*	Mean (± SD) or Spearman Correlation Coefficient	*P*
Height SDS	PRT	36	−1.19 (± 1.22)	.020
	XRT	23	−2 (± 1.35)	
	Primary dose[a]	59	−0.241	.066
BMI SDS	PRT	36	0.6 (± 1.08)	.453
	XRT	24	0.38 (± 1.17)	
	2000–2004[b]	16	1.01 (± 0.75)	.036
	2005–2009	44	0.33 (± 1.18)	
	Age	60	−0.257	.048

RT type and other covariates with $P \leq .10$ are presented.
P-value is calculated by ANOVA or Spearman rank correlation where appropriate.
[a]As continuous.
[b]Represents year of diagnosis.

models (Supplementary Table S1). Forty-six patients matched by propensity score were identified, including 23 patients for each cohort treated with PRT and XRT. PRT remained a significant predictor of reduced risk of hypothyroidism, sex hormone deficiency, and need for endocrine replacement therapy and remained significantly associated with greater height SDS at last follow-up under the propensity adjusted models (Table 5).

Discussion

This report of late endocrine dysfunction among proton- and photon-treated children with standard risk medulloblastoma represents the first direct clinical comparison of late endocrine effects among pediatric patients treated with proton or photon craniospinal radiotherapy. The results demonstrate a statistically significant association between the use of proton therapy and a reduced incidence of hypothyroidism and sex hormone deficiency, a reduced need for endocrine replacement therapy, and greater height SDS at last follow-up among medulloblastoma

Table 4. Multivariable analysis of endocrine dysfunction

Outcome	Covariate	Odds Ratio (95% CI) or Parameter Estimate (95% CI)	*P*
Hypothyroidism	PRT vs XRT	0.13 (0.04–0.41)	<.001
	CSI dose	1.75 (1.04–2.94)	.036
Growth hormone deficiency	PRT vs XRT	0.81 (0.26–2.59)	.728
	Male vs female	3.80 (1.29–11.17)	.015
	Classic histology vs others	7.07 (1.66–30.19)	.008
	Age at diagnosis	0.83 (0.71–0.97)	.018
Sex hormone deficiency	PRT vs XRT	0.06 (0.01–0.55)	.013
	Male vs female	0.31 (0.06–1.63)	.167
Endocrine replacement therapy	PRT vs XRT	0.30 (0.09–0.99)	.047
	Male vs female	2.82 (0.94–8.42)	.064
	Classic histology vs others	4.42 (1.14–17.18)	.032
	Age at diagnosis	0.90 (0.78–1.04)	.164
	CSI dose	1.30 (0.92–1.84)	.134
Height SDS[a]	PRT vs XRT	0.89 (0.24–1.54)	.008
	Residual disease after surgery <1.5 cm^2 vs none	−0.77 (−1.81–0.28)	.153

Seventy-seven observations were used in the model. Backward variable selection method with an alpha level of 0.2 was used for all models. Models were stratified by date of diagnosis. The following variables were removed from the model when not listed: age, date of diagnosis, gender, histology, location of RT boost, CSI dose, and residual disease after surgery.
[a]For analysis of height SDS, 59 observations were used; values are parameter estimate (95% CI).

Table 5. Propensity score analysis of endocrine outcomes according to RT type

Outcome	Model	PRT vs XRT Odds Ratio (95% CI) or Parameter Estimate (95% CI)	*P*
Hypothyroidism	PS adjusted	0.13 (0.04–0.42)	<.001
	IPTW	0.13 (0.05–0.38)	<.001
	1:1 Matching	0.07 (0.01–0.54)	.011
Sex hormone deficiency	PS adjusted	0.07 (0.01–0.73)	.026
	IPTW	0.07 (0.01–0.70)	.023
	1:1 Matching	N/A[a]	
Endocrine replacement therapy	PS adjusted	0.36 (0.12–1.08)	.068
	IPTW	0.35 (0.13–0.93)	.036
	1:1 Matching	0.25 (0.05–1.18)	.080
Height SDS[b]	PS adjusted	0.82 (0.13–1.51)	.020
	IPTW	0.82 (0.18–1.46)	.012
	1:1 Matching	0.86 (0.15–1.56)	.017

Abbreviations: PS, propensity score; IPTW, inverse probability of treatment weighting.
The propensity score of being treated with PRT (vs XRT) was estimated using a multivariable logistic regression model including gender, date of diagnosis, histology, location of RT boost, CSI dose, and age at diagnosis. Forty-six observations were used for 1:1 matching, 77 observations for other models.
[a]Due to poor fit caused by a quite small number of events in the matched sample.
[b]For analysis of height SDS, 39 observations were used for 1:1 matching and 59 observations for other models; values are parameter estimate (95% CI).

survivors. These findings are of great clinical importance, as a presumed benefit in late radiation associated sequelae has been a primary driving force for the increasing use of proton therapy among children, though comparative clinical data are limited.

The photon cohort in this series serves as a good benchmark for comparison with proton outcomes, considering that the photon endocrine outcomes reported here are similar to those previously reported in the published literature. Hypothyroidism is recognized as one of the most common endocrinopathies associated with CSI, and the 65% incidence reported here is consistent with previous reports citing hypothyroidism rates in the range of 60%–80% among patients who received standard dose, conventionally fractionated CSI plus chemotherapy.[8,23–25] The incidence of hypothyroidism was associated with CSI dose in this analysis, and previous studies have also demonstrated a reduced risk of hypothyroidism with lower CSI doses.[26] The incidences of adrenal insufficiency, precocious puberty, and sex hormone deficiency in the photon cohort here were 8%, 16%, and 19%, respectively. These rates are similar to those previously published in the literature, which have been in the ranges of 12.5%–25%[26–28] for adrenal insufficiency, 11%–16%[6,26] for precocious puberty, and 20%–50% for sex hormone deficiency.[1,2,29] While additional factors such as patient age, time since treatment, dose of radiotherapy, and other therapies received can affect the risk of endocrine dysfunction and may account for differences between series,[1,8,10,26,30,31] the similar patient characteristics and uniform treatment received between the proton and photon cohorts in this report further establish a framework for evaluating the effect of RT type on these endocrine outcomes.

However, analysis of GHD according to RT type may have been limited by institutional differences in GH testing. Among the photon cohort, patients were offered testing if there was clinical

suspicion of the condition, but testing may not have been undertaken if the patient/family actively declined the treatment prior to testing. Family willingness to undergo GH replacement may have been impacted by social factors such as cost or a fear of the potential impact on tumor recurrence or second malignancy risk.[32] This may have artificially lowered the GHD reported, as patients may have had clinical evidence of GHD but may not have undergone the confirmatory testing required to make the diagnosis. In contrast, GH stimulation testing was recommended for all patients with a clinical suspicion of GHD treated on the proton phase II study used for comparison. Approximately 57% of patients treated with photon therapy developed GHD in this analysis. While this rate is similar to the 53% incidence of GHD reported among the medulloblastoma patients from the Childhood Cancer Survivor Study,[1] it is less than the 75% incidence rate that would be predicted based on modeling data taking into account the cranial radiotherapy doses received and the median follow-up of greater than 5 years.[33] Growth hormone deficiency was more common among male patients with classic histology in this analysis. This may reflect selection biases in the diagnosis and treatment of GHD, as there may have been less of a concern for risk of tumor recurrence with classic histology and a greater perceived negative impact of reduced height in males. Despite any potential biases according to histology, gender, or institution, proton patients were found to have a significantly greater height SDS than photon patients. Because the entire vertebral bodies are included in the target volume in growing children with both modalities, one would not expect this to be related to differing adverse effects of radiotherapy on sitting height. Rather, this suggests that subtle differences in the effects of RT modality on GH function may exist. The analysis of height SDS in this study is also limited in that height at last follow-up was not available for all 77 patients ($n = 59$ for height SDS), and further analysis of the effect of proton versus photon RT on height as well as the incidence of GHD is warranted.

Additional limitations of this study include that the proton patients were treated on a phase II study with prospective data collection, while data for the photon cohort were collected retrospectively. Because the patients were treated and followed at different institutions, biases in endocrine testing or diagnoses may have impacted the results. However, because only patients who underwent routine endocrine screening were included for analysis, bias should be limited. Time to event analysis was not performed because the time of first onset of each endocrine dysfunction was not reliably recorded in the photon cohort. In order to account for the possible effect of varying follow-up times, the multivariable analysis was stratified by follow-up time, and date of diagnosis was included as a variable in propensity analysis. Although baseline endocrine function was not uniformly tested, the tumor located within the PF would not be expected to impact hypothalamic-pituitary, thyroid, or gonadal function. Neither the proton nor the photon data distinguished whether hypothyroidism or sex hormone deficiency was primary or central in origin, though both are applicable endpoints, as dose delivered directly to the thyroid and gonads as well as the HPA has been demonstrated to be reduced with proton therapy,[12–14] and this does not impact the validity of the data.

Strengths of this analysis include the assessment of well-matched proton and photon cohorts who were treated uniformly with radiation and chemotherapy over a similar time period from 2000 to 2009, with mature follow-up and routine endocrine screening. Though the median age at diagnosis of the proton cohort was slightly younger than the photon cohort, this would only have been expected to lead to higher rates of endocrine dysfunction in proton patients, as younger age has been previously associated with an increased risk of some endocrinopathies.[24] Furthermore, the associations found between proton therapy and the reduced risk of multiple endocrine outcomes were maintained on multivariable and propensity score adjusted analyses.

In conclusion, the use of proton therapy was significantly associated with a reduced risk of hypothyroidism and sex hormone deficiency, a reduced need for any endocrine replacement therapy, and greater height SDS at last follow-up among matched cohorts of medulloblastoma survivors treated similarly with chemotherapy and proton or photon RT. The use of proton therapy should be considered to minimize the radiation-associated endocrine sequelae for medulloblastoma patients. Further analysis of GHD and nonhormonally mediated alterations of growth among proton- and photon-treated patients is required.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Journal* online (http://neuro-oncology.oxfordjournals.org/).

Funding

This work was supported in part by the National Cancer Institute, award number P01CA021239, and the Federal Share of program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and Treatment Center. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Conflict of interest statement. Dr Tarbell's spouse is on the medical advisory board of ProCure Treatment Centers, Inc. and holds stock options in ProCure.

Unpublished material under reference: Yock T, Yeap BY, Ebb D, et al. Pediatric medulloblastoma: clinical outcomes from a prospective phase II study of proton radiotherapy. *Lancet Oncol*. 2015.

References

1. Gurney JG, Kadan-Lottick NS, Packer RJ, et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. *Cancer*. 2003; 97(3):663–673.
2. Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *N Engl J Med*. 1993; 328(2):87–94.
3. Fossati P, Ricardi U, Orecchia R. Pediatric medulloblastoma: toxicity of current treatment and potential role of proton therapy. *Cancer Treat Rev*. 2009;35(1):79–96.

4. Mailhot Vega RB, Kim J, Bussiere M, et al. Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *Cancer*. 2013; 119(24):4299–4307.
5. Ahmed SR, Shalet SM, Campbell RH, et al. Primary gonadal damage following treatment of brain tumors in childhood. *J Pediatr*. 1983;103(4):562–565.
6. DeWire M, Green DM, Sklar CA, et al. Pubertal development and primary ovarian insufficiency in female survivors of embryonal brain tumors following risk-adapted craniospinal irradiation and adjuvant chemotherapy. *Pediatr Blood Cancer*. 2014; doi:10.1002/pbc.25274.
7. Brauner R, Czernichow P, Rappaport R. Precocious puberty after hypothalamic and pituitary irradiation in young children. *N Engl J Med*. 1984;311(14):920.
8. Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. *J Clin Oncol*. 2008;26(7):1112–1118.
9. Lauro C, Macy ME, Zeitler P, et al. The relationship between thyroid dose and diagnosis of primary hypothyroidism in pediatric brain tumor patients receiving craniospinal irradiation. *J Pediatr Endocrinol Metab*. 2014;27(3-4):299–303.
10. Green DM, Kawashima T, Stovall M, et al. Fertility of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009;27(16):2677–2685.
11. Merchant TE, Goloubeva O, Pritchard DL, et al. Radiation dose-volume effects on growth hormone secretion. *Int J Radiat Oncol Biol Phys*. 2002;52(5):1264–1270.
12. Lee CT, Bilton SD, Famiglietti RM, et al. Treatment planning with protons for pediatric retinoblastoma, medulloblastoma, and pelvic sarcoma: how do protons compare with other conformal techniques? *Int J Radiat Oncol Biol Phys*. 2005;63(2):362–372.
13. Miralbell R, Lomax A, Russo M. Potential role of proton therapy in the treatment of pediatric medulloblastoma/primitive neuro-ectodermal tumors: spinal theca irradiation. *Int J Radiat Oncol Biol Phys*. 1997;38(4):805–811.
14. St Clair WH, Adams JA, Bues M, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2004;58(3):727–734.
15. Perez-Andujar A, Newhauser WD, Taddei PJ, et al. The predicted relative risk of premature ovarian failure for three radiotherapy modalities in a girl receiving craniospinal irradiation. *Phys Med Biol*. 2013;58(10):3107–3123.
16. Yock TI, Yeap BY, Ebb D, et al. A phase II trial of proton radiotherapy for medulloblastoma: preliminary results. *J Clin Oncol*. 2010;28(15 suppl 28):9507. (oral presentation and abstract)
17. Pai Panandiker A, Ning H, Likhacheva A, et al. Craniospinal irradiation with spinal IMRT to improve target homogeneity. *Int J Radiat Oncol Biol Phys*. 2007;68(5):1402–1409.
18. Children's Hospital Boston Growth Calculator v2.01. http ://growthcalc.chip.org/GrowthCalc 2014.
19. Rosenbaum PR, Rubin DP. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1): 41–55.
20. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Stat Med*. 2006;25(12):2084–2106.
21. Rosenbaum PR. Model-based direct adjustment. *J Am Stat Assoc*. 1987;82(398):387–394.
22. Austin PC. The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. *Med Decis Making*. 2009;29(6):661–677.
23. Massimino M, Gandola L, Collini P, et al. Thyroid-stimulating hormone suppression for protection against hypothyroidism due to craniospinal irradiation for childhood medulloblastoma/primitive neuroectodermal tumor. *Int J Radiat Oncol Biol Phys*. 2007;69(2):404–410.
24. Paulino AC. Hypothyroidism in children with medulloblastoma: a comparison of 3600 and 2340 cGy craniospinal radiotherapy. *Int J Radiat Oncol Biol Phys*. 2002;53(3):543–547.
25. Ricardi U, Corrias A, Einaudi S, et al. Thyroid dysfunction as a late effect in childhood medulloblastoma: a comparison of hyperfractionated versus conventionally fractionated craniospinal radiotherapy. *Int J Radiat Oncol Biol Phys*. 2001; 50(5):1287–1294.
26. Xu W, Janss A, Packer RJ, et al. Endocrine outcome in children with medulloblastoma treated with 18 Gy of craniospinal radiation therapy. *Neuro Oncol*. 2004;6(2):113–118.
27. Spoudeas HA, Charmandari E, Brook CG. Hypothalamo-pituitary-adrenal axis integrity after cranial irradiation for childhood posterior fossa tumours. *Med Pediatr Oncol*. 2003; 40(4):224–229.
28. Rose SR, Danish RK, Kearney NS, et al. ACTH deficiency in childhood cancer survivors. *Pediatr Blood Cancer*. 2005;45(6):808–813.
29. Uday S, Murray RD, Picton S, et al. Endocrine sequelae beyond 10 years in survivors of medulloblastoma. *Clin Endocrinol (Oxf)*. 2015; 83(5):663–670.
30. Patterson BC, Truxillo L, Wasilewski-Masker K, et al. Adrenal function testing in pediatric cancer survivors. *Pediatr Blood Cancer*. 2009;53(7):1302–1307.
31. Olshan JS, Gubernick J, Packer RJ, et al. The effects of adjuvant chemotherapy on growth in children with medulloblastoma. *Cancer*. 1992;70(7):2013–2017.
32. Patterson BC, Chen Y, Sklar CA, et al. Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: a report from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab*. 2014;99(6):2030–2037.
33. Merchant TE, Rose SR, Bosley C, et al. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. *J Clin Oncol*. 2011;29(36):4776–4780.