Title

Post-treatment neuroendocrine outcomes among pediatric brain tumor patients: Is there a difference between proton and photon therapy?

Authors

Yip, Anthony T
Yu, Justin D
Huynh-Le, Minh-Phuong
et al.

Publication Date

2022-05-01

DOI

10.1016/j.ctro.2022.02.010

Peer reviewed

Clinical and Translational Radiation Oncology 34 (2022) 37–41

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Post-treatment neuroendocrine outcomes among pediatric brain tumor patients: Is there a difference between proton and photon therapy?

Anthony T. Yip [a,1], Justin D. Yu [a,1], Minh-Phuong Huynh-Le [a,d], Mia Salans [a], Soumya Unnikrishnan [a], Alexander S Qian [a], Ronghui Xu [b], Ryan Kaner [c], Iain MacEwan [a], John R. Crawford [c], Jona A. Hattangadi-Gluth [a,*]

[a] Department of Radiation Medicine and Applied Sciences, UC San Diego, 3855 Health Sciences Dr., #0843 La Jolla, CA 92093, USA
[b] Department of Family Medicine and Public Health and the Department of Mathematics, 9500 Gilman Dr, La Jolla, CA 92093, USA
[c] Rady Children's Hospital, 3020 Children's Way, San Diego, CA 92123, USA
[d] Radiation Oncology, The Brooklyn Cancer Center, 121 Dekalb Ave, Brooklyn, NY 11201, USA

ARTICLE INFO

Keywords:
Pediatric
Brain tumor
Neuroendocrine
Proton
Photon
Radiation therapy

ABSTRACT

Purpose: Pediatric brain tumor patients are vulnerable to radiotherapy (RT) sequelae including endocrinopathies. We compared post-RT neuroendocrine outcomes between pediatric brain tumor patients receiving photons (XRT) versus protons (PRT).

Methods: Using a prospectively maintained single-institution database, we analyzed 112 pediatric primary brain tumor patients (80 XRT, 32 PRT) from 1996 to 2019. Patient/treatment characteristics and endocrinopathy diagnoses (growth hormone deficiency [GHD], sex hormone deficiency [SHD], hypothyroidism, and requirement of hormone replacement [HRT]) were obtained via chart review. Univariable/multivariable logistic regression identified neuroendocrine outcome predictors. Time-adjusted propensity score models accounted for treatment type. Craniospinal irradiation (CSI) patients were evaluated as a sub-cohort.

Results: Median follow-up was 6.3 and 4.4 years for XRT and PRT patients respectively. Medulloblastoma was the most common histology (38%). Half of patients (44% in XRT, 60% in PRT) received CSI. Common endocrinopathies were GHD (26% XRT, 38% PRT) and hypothyroidism (29% XRT, 19% PRT). CSI cohort PRT patients had lower odds of hypothyroidism (OR 0.16, 95% CI[0.02–0.87], $p = 0.045$) on multivariable regression and propensity score analyses. There were no significant differences in endocrinopathies in the overall cohort and in the odds of GHD or HRT within the CSI cohort. SHD developed in 17.1% of the XRT CSI group but did not occur in the PRT CSI group.

Conclusion: Endocrinopathies were common among pediatric brain tumor survivors. Among CSI patients, PRT was associated with lower risk of hypothyroidism, and potentially associated with lower incidence of SHD. Future studies should involve collaborative registries to explore the survivorship benefits of PRT.

Introduction

While brain radiotherapy (RT) plays a critical role in the management of pediatric brain tumors, it is also associated with neuroendocrine sequalae such as growth, thyroid, and sex hormone deficiencies, specifically via radiation effects on the hypothalamic-pituitary axis. Younger patients show higher rates of post-radiation endocrinopathy [1–3], suggesting that children are especially vulnerable. Diagnosis of growth or sex hormone deficiency during childhood can precipitate psychosocial stressors including suboptimal growth or failure to transition through puberty[4,5]. Unsurprisingly, patients who develop endocrinopathies at younger ages have shown poorer quality of life in areas including emotional stability and social functionality[6,7]. These effects are maintained even throughout adulthood and are associated

* Corresponding author.
E-mail addresses: a3yip@health.ucsd.edu (A.T. Yip), jdy002@ucsd.edu (J.D. Yu), mhuynhle@nycancer.com (M.-P. Huynh-Le), msalans@health.ucsd.edu (M. Salans), sunnikri@health.ucsd.edu (S. Unnikrishnan), asqian@health.ucsd.edu (A.S. Qian), rxu@health.ucsd.edu (R. Xu), rkaner@rchsd.org (R. Kaner), imacewan@health.ucsd.edu (I. MacEwan), JCrawford@rchsd.org (J.R. Crawford), jhattangadi@health.ucsd.edu (J.A. Hattangadi-Gluth).
[1] Co-first authorship.

https://doi.org/10.1016/j.ctro.2022.02.010
Received 11 February 2022; Accepted 22 February 2022
Available online 25 February 2022

with increased lifetime medical costs[6,8].

The extent of post-radiation endocrinopathy appears to be a dose-dependent- phenomenon, with growth hormone deficiency being the most common[2,9]. This differential sensitivity suggests potential benefits from radiation techniques that offer increased sparing of the hypothalamic-pituitary axis. Compared to photon radiation (XRT), proton radiation (PRT) offers the potential for reduced radiation toxicity due to the Bragg Peak phenomenon[10]. Similar survival outcomes have been observed in XRT and PRT brain tumor cohorts[11–14], though it is unclear if PRT offers improvements in risks of long-term sequelae. Dosimetric studies in medulloblastoma patients have shown that proton craniospinal irradiation (CSI) delivers less hypothalamic-pituitary toxicity compared to conventional photon or IMRT treatments [15,16]. There is a lack of randomized data for photon versus proton CSI in pediatric brain tumor patients; therefore, an understanding of radiation-associated endocrinopathy in this patient population must rely on cross-sectional and retrospective cohort studies. Two previous studies have examined pediatric neuroendocrine outcomes following proton versus photon cranial radiation with mixed results. One study of standard risk medulloblastoma patients[3] reported a lower risk of hypothyroidism, sex hormone deficiency, and requirement of hormone replacement therapy among patients receiving proton therapy. Another study [17], however, found no significant differences by modality.

Methods

Patients

We examined neuroendocrine outcomes following PRT and XRT in a cohort of pediatric primary brain tumor patients including medulloblastoma patients and other brain tumor types (see Table 1). Using a prospectively maintained pediatric tumor database from Rady Children's Hospital, we analyzed 112 consecutively treated pediatric patients with primary brain tumors treated from 1996 to 2019 with approval from the University of California Institutional Review Board. Inclusion criteria included diagnosis of primary brain tumor, treatment with either XRT or PRT, age $<$ 21 years at time of radiotherapy (RT), follow-up $\geq$ 6 months (time from RT completion to last documented appointment), available documentation of radiation treatment plan, and documented neuroendocrine follow-up. Patient, tumor, and treatment characteristics as well as primary outcomes were collected via chart review. To minimize bias from manual collection, coded search queries were used whenever possible. Patient related covariates included gender, race, baseline performance score (Lansky/Karnofsky), and socioeconomic status (SES). Tumor- and treatment-related covariates included tumor histology, type of surgical resection, treatment with CSI, hydrocephalus treated with ventriculoperitoneal (VP) shunt, systemic therapy, age at RT, total RT dose, RT type (XRT vs PRT), and follow-up time (end of RT to last documented neuroendocrine visit). SES was represented by percent poverty and median income, which were derived from patient zip codes using 2018 census data[18,19]. Results were categorized as binary variables with cutoffs (13% poverty, median income of $75,000) based on average results within California[18,19].

Outcomes

Neuroendocrine outcomes included development of hypothyroidism, growth hormone deficiency (GHD), sex hormone deficiency (SHD), and requirement of hormone replacement therapy (HRT). Sex hormone deficiency was defined as deficiency in LH (lutenizing hormone), FSH (follicle-stimulating hormone), estrogen/progesterone or testosterone. Outcomes were recorded as binary variables and based on official documentation in the medical record by the treating endocrinologist or oncologist.

Table 1
Patient Cohort Characteristics.

Covariate	Radiation Type XRT (N = 80)	PRT (N = 32)	p-value[a]
Gender	31	18	0.098
Female	(38.8%)49	(56.3%)14	
Male	(61.2%)	(43.7%)	
Ethnicity	34	10	0.29
Hispanic	(42.5%)46	(32.3%)22	
Non-Hispanic	(57.5%)	(68.8%)	
Tumor Histology	26	16	0.090
Medulloblastoma	(32.5%)54	(50.0%)16	
Other[b]	(67.5%)	(50.0%)	
Resection Type[c]	38 (52.1)	19	0.519
GTR	35	(61.3%)12	
Near/STR & Biopsies	(47.9)	(38.7%)	
Craniospinal Irradiation	35	18	0.198
Yes	(44.3%)44	(60.0%)12	
No	(55.7%)	(40.0%)	
VP Shunt	32	16	0.292
Yes	(40.0%)48	(51.6%)15	
No	(60.0%)	(48.4%)	
Baseline Performance Score	4	4	0.713
$<$70	(13.8%)25	(18.2%)18	
$\geq$70	(86.2%)	(81.8%)	
Systemic Therapy	65	29	0.145
Yes	(81.3%)15	(93.5%)2	
No	(18.8%)	(6.5%)	
Age at RT (years)	8.57	5.51	**0.034***
Median (IQR)	(1.20 – 20.0)	(1.19, 17.4)	
Prescription RT Dose (Gy)	54.0	54.0	0.882
Median (IQR)	(20.0 – 60.0)	(30.0 – 59.4)	
Follow-up (years)	6.3	4.4	**0.052**
Median (IQR)	(0.5 – 19.1)	(0.9 – 18.7)	
Percent Poverty[d]	38	20	0.210
$<$13%	(48.1%)41	(62.5%)12	
$\geq$13%	(51.9%)	(37.5%)	
Median Income[d]	46	13	0.099
$<$$75,000	(58.2%)33	(40.6%)19	
$\geq$$75,000	(41.8%)	(59.4%)	

*p-value $<$ 0.05.
Abbreviations: XRT: photon radiotherapy; PRT, proton radiotherapy; GTR, gross tumor resection; VP, ventriculoperitoneal; RT, radiotherapy; Gy, gray; IQR: interquartile range.
[a] Categorical and continuous data were respectively analyzed using Fisher's exact and Wilcoxan rank-sum tests.
[b] Other tumor histology: astrocytoma (17), ependymoma (14), germ cell (13), glioma (11), ATRT (5), pineoblastoma (3), NF-2 associated vestibular schwannoma (2), chordoma (1), hemangioendothelioma (1), meningioma (1), neurocytoma (1), PNET (1).
[c] GTR was determined by direct verbiage in chart review. Other includes near/sub-total resection, as well as biopsies and unspecified resection.
[d] Calculated from patient zip codes via US census data from 2018. Cutoff levels of 13% poverty and median income of $75,000 were determined based on average results within California.

Statistical analysis

Patient, tumor, and treatment covariates were compared between XRT and PRT cohorts using Fisher's exact and Wilcoxon rank sum tests. We examined associations between covariates and each neuroendocrine outcome using univariable logistic regression. We performed multivariable logistic regression to assess the relationship between radiation modality and each neuroendocrine outcome. Multivariable models adjusted for follow-up time and included radiation modality, covariates significant on univariable analysis, and covariates that were significantly different between treatment cohorts. Regression coefficients with a p-value $<$ 0.05 in the final multivariable model were deemed significant. We used a false discovery rate correction to adjust for multiple comparisons.

To account for confounders between radiation groups, we also performed a separate propensity score analysis using inverse probability of

treatment weighting (IPTW) via the R package 'twang'.[20] Assigning radiation modality as the outcome, we used a generalized boosted tree model to calculate propensity scores. We assessed balance between treatment and adjusted control groups using absolute standardized mean differences for each covariate.

To address cohort heterogeneity by treatment fields and to explore the differences among patients receiving CSI, we performed a sub-analysis on patients who received craniospinal irradiation. We examined the same outcomes with the same statistical analysis methods restricted to patients receiving CSI.

Results

Patient, tumor, and treatment characteristics compared by radiation modality are shown in Table 1. Photon (n = 80) and proton (n = 32) patients mainly differed in age (median: 8.6 years XRT [1.20–20.0], 5.5 years PRT [1.19–7.4]; p = 0.034) and follow-up time (median: 6.3 years XRT [0.5–19.1], 4.4 years PRT [0.9–18.7]; p = 0.052). Tumor histology between cohorts was similar, with the most common diagnoses being medulloblastoma (38%), astrocytoma (15.2%), and ependymoma (12.5%). Median total RT dose was 54 Gy (range 20–60 XRT; 30.59.4 PRT) in both groups with about half of patients (44% in XRT, 60% in PRT) receiving CSI. Cohorts were otherwise similar regarding gender, race, resection type, baseline performance, systemic therapy, and SES.

Endocrinopathy outcomes

Table 2 summarizes the rates of post-treatment endocrinopathies. None of the patients had documented endocrinopathy at baseline (prior to radiotherapy). The overall incidence of any post-treatment endocrinopathy was 38.4% (36.2% XRT, 43.8% PRT), with the most common endocrinopathies being growth hormone deficiency (26% XRT, 38% PRT) and hypothyroidism (29% XRT, 19% PRT). Incidence of sex hormone deficiency was 11.6% (13.8% XRT, 6.3% PRT). Hormone replacement therapy was prescribed to 32.1% of patients (30.0% XRT, 37.5% PRT).

Logistic regression analysis

Univariable and multivariable logistic regression analyses examined the likelihood of neuroendocrine outcome accounting for relevant covariates such as treatment modality, histology, and total prescription dose. Treatment type (proton versus photons) was not significantly associated with developing hypothyroidism, growth hormone deficiency, sex hormone deficiency, or hormone replacement therapy outcomes (all p > 0.05) in both univariable and multivariable models.

In the overall cohort, there were no significant differences in the outcomes between XRT and PRT groups. Multivariable models showed that non-medulloblastoma patients had lower odds of developing hypothyroidism (OR 0.26, p = 0.005) or growth hormone deficiency (OR 0.20, p = 0.002), or of requiring hormone replacement therapy (OR 0.18, p < 0.001); these results remained significant after adjusting for multiple comparisons (Table 3). Greater follow-up time was positively associated with development of growth hormone deficiency (OR 1.18, p = 0.004) and sex hormone deficiency (OR 1.18, p = 0.032). After correction for multiple comparisons, follow-up time remained significantly associated with growth hormone deficiency. The usage of a VP shunt was positively associated with hypothyroidism (OR 2.66, p = 0.04) and a higher prescribed RT dosage was associated with decreased odds of developing sex hormone deficiency (OR 0.93, p = 0.029) through after correction for multiple comparisons, neither association was significant. Results of regression analyses are summarized in Table 3.

Sub-analysis of CSI patients

The CSI cohort was comprised largely of medulloblastoma patients (74% of the XRT recipients, 89% of the PRT recipients); other cancer histology included astrocytoma, ATRT, PNET, germinoma, glioma, and pineoblastoma. XRT (n = 35) and PRT (n = 18) groups only differed in gender (74% males XRT, 44% males PRT) and follow-up time (median: 7.0 years XRT, 4.6 years PRT). However, there were no statistically significant differences between any of the variables.

Endocrinopathy outcomes

The overall incidence of endocrinopathy was 60.0% in photon patients and 61.1% in proton patients, with the most common endocrinopathy again being growth hormone deficiency (46% XRT, 50% PRT) and hypothyroidism (49% photon, 17% proton). None of the PRT patients developed sex hormone deficiency, compared to 17.1% of the XRT patients. Hormone replacement therapy was prescribed to 48.6% of XRT and 50.0% of PRT patients.

Logistic regression analysis

After adjusting for follow-up time, PRT was associated with lower odds of hypothyroidism compared with XRT on both univariable (OR

Table 2
Incidence of Endocrinopathy.

Endocrinopathy	Whole Cohort XRT (n = 80)	PRT (n = 32)	CSI Cohort XRT (n = 35)	PRT (n = 18)
Hypothyroidism	23	6	17	3
Yes	(28.8%)57	(18.8%)26	(48.6%)18	(16.7%)15
No	(71.3%)	(81.3%)	(51.4%)	(83.3%)
Growth Hormone	21	12	16	9
Deficiency	(26.3%)59	(37.5%)20	(45.7%)19	(50.0%)9
Yes	(73.8%)	(62.5%)	(54.3%)	(50.0%)
No				
Sex Hormone Deficiency	11	2	6	0
Yes	(13.8%)69	(6.3%)30	(17.1%)29	(0%)18
No	(86.3%)	(93.8%)	(82.9%)	(100%)
Hormone Replacement	24	12	17	9
Therapy	(30.0%)56	(37.5%)20	(48.6%)18	(50.0%)9
Yes	(70.0%)	(62.5%)	(51.4%)	(50.0%)
No				

Footer:
Abbreviations: XRT, photon radiotherapy; PRT, proton radiotherapy

Table 3
Significant associations between tumor histology and endocrine outcomes.

Endocrinopathy	Univariable Other vs Medulloblastoma OR (95% CI)	p-value	Multivariable[a] Other vs Medulloblastoma OR (95% CI)	p-value
Hypothyroidism	0.25 (0.10, 0.59)	0.002*	0.26 (0.09, 0.66)	0.005*
Growth Hormone Deficiency	0.14 (0.05, 0.33)	<0.001*	0.20 (0.07, 0.54)	0.002*
Hormone Replacement Therapy	0.13 (0.05, 0.30)	<0.001*	0.18 (0.07, 0.44)	<0.001*

Footer:
Abbreviations: XRT, photon radiotherapy; PRT, proton radiotherapy; OR: odds ratio
[a] Time adjusted multivariable model including radiation modality and covariates significant on univariable analysis (Endocrinopathy ~ Radiation modality + time + covariates)
[b] Other tumor histology: 11 glioma, 5 ATRT, 3 pineoblastoma, 2 NF-2, 1 chordoma, 1 hemangioendothelioma, 1 meningioma, 1 neurocytoma, 1 PNET
* P < 0.05 and remained significant after false discovery rate correction

0.21, p = 0.03) and multivariable (OR 0.16, p = 0.045) analysis. Univariable and multivariable models showed no significant association between radiation modality and growth hormone deficiency or requirement of hormone replacement therapy (all p > 0.05). We were unable to perform regression analysis for sex hormone deficiency given the lack of events within the PRT cohort. Results are summarized in Table 4.

Multivariable models adjusted for follow-up time showed that cancer histology and follow-up time were significantly associated with neuroendocrine outcomes. Non-medulloblastoma patients had lower odds of requiring hormone replacement therapy (OR 0.08, p = 0.026). Greater follow-up time was positively associated with growth (OR 1.31, p = 0.005) and sex hormone deficiencies (OR 1.43, p = 0.013).

Propensity score analysis

Within the CSI cohort, propensity score analysis using IPTW showed that PRT was again associated with lower odds of developing hypothyroidism (OR 0.086, p = 0.023) compared with XRT. Radiation modality was not otherwise associated with growth hormone deficiency or hormone replacement therapy (all p > 0.05). Results are summarized in Table 5.

Discussion

In this study, we compared neuroendocrine outcomes in a cohort of pediatric primary brain tumor patients following either photon or proton radiation after controlling for follow-up time. There were no significant differences in neuroendocrine outcomes in the overall cohort; however, a sub-analysis of patients receiving CSI showed that compared to XRT, PRT was associated with lower odds of developing hypothyroidism across multiple statistical approaches. Furthermore, non-medulloblastoma patients had lower odds of developing hypothyroidism, growth hormone deficiency, and requiring hormone replacement therapy. This is likely attributed to the effects of CSI, rather than an inherent endocrinopathy risk, as CSI is the standard of care for medulloblastoma patients. Our findings support the continued use of protons for CSI as needed in pediatric brain tumor patients to reduce future risk of endocrinopathy.

Within the CSI cohort, the incidence of hypothyroidism was 49% (XRT) and 17% (PRT) at a median follow-up of 7.0 and 4.6 years respectively; these rates are consistent with those previously reported in pediatric medulloblastoma cohorts[2,3,17,21]. Compared to XRT, PRT CSI was associated with significantly lower odds of developing hypothyroidism on multivariable and IPTW propensity score adjusted analysis. The consistency between several statistical methods provides strong evidence to support our findings. Additionally, similar results were reported by Eaton et al[3] in a cohort of standard-risk medulloblastoma patients. The lower risk of hypothyroidism observed among patients receiving PRT CSI may be attributed to decreased hypothalamic-pituitary radiation during boost treatments and decreased thyroid exposure from spinal field exit doses[16]. Of note, our outcomes did not distinguish between primary and central hypothyroidism. In a prior cohort of pediatric medulloblastoma patients, Bielamowicz et al [17] reported no statistical association between radiation modality and the risk of overall, primary, and central hypothyroidism. This discrepancy with our findings for overall hypothyroidism may be explained by heterogeneity in tumor location or types in our study, as we analyzed other tumor types besides medulloblastoma. Similarly, variation in the risk of hypothyroidism and requirement for hormone therapy may be due to the differences in dose to the pituitary-hypothalamic axis.

Whereas 17.1% in the XRT CSI cohort developed sex hormone deficiency, no patients in the PRT CSI cohort were diagnosed with sex hormone deficiency. Although this difference was encouraging, we were unable to perform regression analysis given the lack of observations within the PRT group. Prior medulloblastoma PRT cohorts studies have reported incidence rates of sex hormone deficiency at 2.5–5.1% (median follow-up ranging from 3 to 7 years)[2,3,21]. Our lack of a finding of sex hormone deficiency among PRT CSI patients in this study could be attributed to the lower age range of our PRT group (4.7 – 12.5) versus the XRT group (4.4 – 16.3), as gonadotropin deficiencies most commonly present during puberty[2]. Although we could not draw conclusions from the numerical differences in our cohort, Eaton et al[3] previously reported superior SHD outcomes with PRT CSI in a cohort of medulloblastoma patients. These findings are consistent with prior studies showing that SHD is often seen after hypothalamic-pituitary doses ≥ 40 Gy[2,23], suggesting that the benefits of PRT sparing are likely more pronounced among patients receiving high RT doses. Lower rates of SHD within PRT patients may also be mediated by lower radiation doses to pelvic structures during CSI[22], preserving gonad function.

Growth hormone deficiency was consistently the most common endocrinopathy in our study. Of the anterior pituitary hormones, growth hormone is the most sensitive to radiation; deficiencies are often noted following hypothalamic-pituitary axis (HPA) doses ≥ 18 Gy[2,23], with one study by Merchant et al[9] reporting a 50% risk at five years with mean hypothalamus doses of only 16.1 Gy. In our study, we found that radiation modality was not associated with GHD, consistent with previous results by Eaton et al[3]. This lack of association can be explained by the large number of medulloblastoma patients in both studies. Because CSI doses for medulloblastoma range from 23.4 Gy (standard-risk) to 36.0 Gy (high-risk), patients are well over the radiation threshold for developing GHD even before boost treatment. Indeed, the probability of developing GHD begins to plateau at higher hypothalamic-pituitary[2] doses, thereby minimizing potential differences between radiation modalities during boost treatments. Compared to photons, protons have been shown to be cost-effective with respect to GHD through avoidance of chronic complications, depending on the difference in hypothalamic

Table 4
Logistic Regression of Endocrinopathy Outcomes, CSI Subset

	Univariable		Multivariable[a]	
Endocrinopathy	PRT vs XRT OR (95% CI)	p-value	PRT vs XRT OR (95% CI)	p-value
Hypothyroidism	0.21 (0.043, 0.782)	**0.030***	0.16 (0.022, 0.872)	**0.045***
GH Deficiency	1.19 (0.377, 3.753)	0.767	2.39 (0.555, 11.695)	0.256
SH Deficiency	[b]	[b]	[b]	[b]
Hormone Replacement Therapy	1.06 (0.336, 3.337)	0.922	0.77 (0.179, 3.288)	0.726

Footer:
Abbreviations: GH, Growth Hormone; SH, Sex Hormone; VP, Ventriculoperitoneal; RT, radiotherapy; Gy, gray; OR, odds ratio.
[a] All multivariable models are adjusted for time
[b] Unable to analyze because sex hormone deficiency was not observed in the proton group
* P < 0.05 shown in bold

Table 5
Endocrine Propensity Score Analysis, CSI cohort.

Outcome	PRT vs XRT Odds Ratio (95%CI)	p-value
Hypothyroidism	0.086 (0.011, 0.665)	**0.023***
Growth Hormone Deficiency	0.650 (0.088, 4.794)	0.675
Sex Hormone Deficiency	[a]	[a]
Required Hormone Replacement Therapy	0.438 (0.069, 2.793)	0.387

Footer:
Abbreviations: PRT, proton radiotherapy; XRT, photon radiotherapy; PS, propensity score
[a] Unable to analyze because sex hormone deficiency was not observed in the proton group
* p-value < 0.05 shown in bold

sparing[8]. Given the potential of protons, future studies could consider investigating differences in GHD outcomes within cohorts receiving only focal radiation.

There are several limitations to this study, including the heterogeneity of our cohort and the retrospective nature of this study. We excluded craniopharyngioma patients to reduce confounding of neuroendocrine outcomes by tumor or surgical effects on the hypothalamic-pituitary axis. Additionally, our sub-analysis of our CSI cohort addressed varying hypothalamic-pituitary axis radiation exposure between patients with diverse tumor types by ensuring that all patients received radiation to the hypothalamic-pituitary axis. Propensity score analysis also allowed us to correct for various pre-treatment confounders. None of the patients had documented baseline endocrinopathies, and we analyzed the CSI cohort separately (mostly medulloblastoma patients), since they are less likely to have pre-radiation endocrine deficiencies[2]. However, we were unable to verify with baseline labs for all subjects as this information was not always available. Because the exact date of onset of neuroendocrine outcomes was not reliably recorded, we were unable to perform time to event analyses. Nevertheless, differences in follow-up time were expected (PRT therapy became more readily available at our institution beginning in 2012) and adjusted for in all analyses. It should be noted, however, that hypopituitarism may take years to develop after RT so differences in follow up time may influence outcomes. Our analysis did not distinguish between traditional X-ray or more conformal methods such as IMRT in the photon cohort; inclusion of less-conformal photon therapy methods may have contributed to greater outcome differences between radiation groups. Finally, we did not have access to each individual radiation plan so unable to analyze dosimetric differences to the pituitary/hypothalamic axis, though we did analyze prescription dose.

In conclusion, our study showed that patients receiving proton CSI for primary brain tumors had a reduced risk of developing hypothyroidism compared to patients receiving photon CSI. Patients receiving proton CSI also had a lower incidence of sex-hormone deficiency. Our findings add to the current literature on pediatric radiation-associated endocrinopathy and suggest that proton CSI is associated with improved neuroendocrine outcomes in a real-world clinical setting. Future prospective comparative studies are needed, especially with collaborative registries such as the Pediatric Proton/Photon Consortium Registry[24], and may provide further evidence on the potential of proton radiation for improving patient outcomes and quality of life.

Funding

This work was supported by the National Institutes of Health (1TL1TR001443 to MS, AY, UL1TR001442 of CTSA funding in support of CTRI, and 1KL2TR001444, UL1TR000100, R01 CA238783-01 to JAH-G). The content is solely the responsibility of the authors and does not necessarily represent the official views of any of the funding agencies, who had no direct role in designing, conducting, or reporting of the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008–2012. Neuro Oncol 2015;17(suppl 4):iv1–62. https://doi.org/10.1093/neuonc/nov189.

[2] Vatner RE, Niemierko A, Misra M, Weyman EA, Goebel CP, Ebb DH, et al. Endocrine Deficiency As a Function of Radiation Dose to the Hypothalamus and Pituitary in Pediatric and Young Adult Patients With Brain Tumors. J Clin Oncol 2018;36(28):2854–62. https://doi.org/10.1200/JCO.2018.78.1492.

[3] Eaton BR, Esiashvili N, Kim S, Patterson B, Weyman EA, Thornton LT, et al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. Neuro Oncol 2016;18(6):881–7. https://doi.org/10.1093/neuonc/nov302.

[4] Thomas JDJ, Monson JP. Adult GH deficiency throughout lifetime. Eur J Endocrinol 2009;161(suppl_1):S97–106. https://doi.org/10.1530/EJE-09-0258.

[5] Vern-Gross TZ, Bradley JA, Rotondo RL, Indelicato DJ. Fertility in childhood cancer survivors following cranial irradiation for primary central nervous system and skull base tumors. Radiother Oncol 2015;117(2):195–205. https://doi.org/10.1016/j.radonc.2015.10.001.

[6] Kendall-Taylor P, Jönsson PJ, Abs R, Erfurth EM, Koltowska-Häggström M, Price DA, et al. The clinical, metabolic and endocrine features and the quality of life in adults with childhood-onset craniopharyngioma compared with adult-onset craniopharyngioma. Eur J Endocrinol 2005;152(4):557–67. https://doi.org/10.1530/eje.1.01877.

[7] Heinks K, Boekhoff S, Hoffmann A, et al. Quality of life and growth after childhood craniopharyngioma: results of the multinational trial KRANIOPHARYNGEOM 2007. Endocrine 2018;59(2):364–72. https://doi.org/10.1007/s12020-017-1489-9.

[8] Mailhot Vega R, Kim J, Hollander A, Hattangadi-Gluth J, Michalski J, Tarbell NJ, et al. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. Cancer 2015;121(10):1694–702. https://doi.org/10.1002/cncr.29209.

[9] Merchant TE, Rose SR, Bosley C, Wu S, Xiong X, Lustig RH. Growth Hormone Secretion After Conformal Radiation Therapy in Pediatric Patients With Localized Brain Tumors. J Clin Oncol 2011;29(36):4776–80. https://doi.org/10.1200/JCO.2011.37.9453.

[10] Cotter SE, McBride SM, Yock TI. Proton Radiotherapy for Solid Tumors of Childhood. Technol Cancer Res Treat 2012;11(3):267–78. https://doi.org/10.7785/tcrt.2012.500295.

[11] Jimenez RB, Sethi R, Depauw N, Pulsifer MB, Adams J, McBride SM, et al. Proton Radiation Therapy for Pediatric Medulloblastoma and Supratentorial Primitive Neuroectodermal Tumors: Outcomes for Very Young Children Treated With Upfront Chemotherapy. Int J Radiat Oncol 2013;87(1):120–6.

[12] Rieken S, Habermehl D, Haberer T, Jaekel O, Debus J, Combs SE. Proton and carbon ion radiotherapy for primary brain tumors delivered with active raster scanning at the Heidelberg Ion Therapy Center (HIT): early treatment results and study concepts. Radiat Oncol 2012;7(1):41. https://doi.org/10.1186/1748-717X-7-41.

[13] MacDonald SM, Sethi R, Lavally B, Yeap BY, Marcus KJ, Caruso P, et al. Proton radiotherapy for pediatric central nervous system ependymoma: Clinical outcomes for 70 patients. Neuro Oncol 2013;15(11):1552–9. https://doi.org/10.1093/neuonc/not121.

[14] Palmer SL, Goloubeva O, Reddick WE, Glass JO, Gajjar A, Kun L, et al. Patterns of Intellectual Development Among Survivors of Pediatric Medulloblastoma: A Longitudinal Analysis. J Clin Oncol 2001;19(8):2302–8. https://doi.org/10.1200/JCO.2001.19.8.2302.

[15] Lee CT, Bilton SD, Famiglietti RM, Riley BA, Mahajan A, Chang EL, 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):362–72. https://doi.org/10.1016/j.ijrobp.2005.01.060.

[16] St. Clair WH, Adams JA, Bues M, Fullerton BC, La Shell S, Kooy HM, 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):727–34. https://doi.org/10.1016/S0360-3016(03)01574-8.

[17] Bielamowicz K, Okcu MF, Sonabend R, Paulino AC, Hilsenbeck SG, Dreyer Z, et al. Hypothyroidism after craniospinal irradiation with proton or photon therapy in patients with medulloblastoma. Pediatr Hematol Oncol 2018;35(4):257–67. https://doi.org/10.1080/08880018.2018.1471111.

[18] United States Census Bureau. American Community Survey: Poverty. American Community Survey 5-year estimates. https://data.census.gov/cedsci/. Published 2018. Accessed February 26, 2020.

[19] United States Census Bureau. American Community Survey: Median Income. 2018 American Community Survey 5-year estimates. https://data.census.gov/cedsci/. Published 2018. Accessed February 26, 2020.

[20] Ridgeway G, McCaffrey D, Morral A, Griffin BA, Burgette L, Cefalu M. twang: Toolkit for Weighting and Analysis of Nonequivalent Groups. 2020. https://cran.r-project.org/package=twang.

[21] Yock TI, Yeap BY, Ebb DH, Weyman E, Eaton BR, Sherry NA, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. Lancet Oncol 2016;17(3):287–98. https://doi.org/10.1016/S1470-2045(15)00167-9.

[22] Ogilvy-Stuart AL, Shalet SM. Effect of radiation on the human reproductive system. Environ Health Perspect 1993;101(suppl 2):109–16. https://doi.org/10.1289/ehp.93101s2109.

[23] Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol 1995;31(5):1113–21. https://doi.org/10.1016/0360-3016(94)00427-M.

[24] Lawell MP, Indelicato DJ, Paulino AC, et al. Proton therapy special feature : Full paper An open invitation to join the Pediatric Proton / Photon Consortium Registry to standardize data collection in pediatric radiation oncology. 2019;(September):1-9.