

# Comparison of Endocrine Outcomes Following Proton and Photon Radiotherapy in Children With Medulloblastoma

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## Clinical Study

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# Abstract

**Background:** Endocrine deficiencies are common following craniospinal irradiation (CSI) in children with brain tumors, but empirical data comparing outcomes following proton (PRT) and photon radiation therapy (XRT) are limited.

**Methods:** This retrospective chart review compared the incidence of hypothyroidism, growth hormone deficiency (GHD), and adrenal insufficiency (AI) in patients with medulloblastoma treated with XRT and PRT between 1997 and 2016. All patients received CSI and had routine endocrine screening labs to evaluate for thyroid dysfunction, GHD, and AI. We used proportional hazards regression to calculate hazard ratios (HR) and 95% confidence intervals (CI) comparing the development of hypothyroidism, AI, and GHD between radiation modalities, adjusting for age at diagnosis, sex, race/ethnicity, and CSI dose.

**Results:** We identified 118 patients with medulloblastoma who were followed for a median of 5.6 years from the end of radiotherapy. Thirty-five (31%) patients developed hypothyroidism, 71 (66%) GHD, and 20 (18%) AI. Compared to PRT, XRT was associated with a higher incidence of primary (28% vs. 6%; HR=4.61, 95% CI 1.2-17.7, p=0.03) and central hypothyroidism (33% vs. 9%; HR 2.35 (0.8-6.8, p=0.12). GHD and AI incidence rates were similar between the groups.

**Conclusions:** Primary and central hypothyroidism occur less often after PRT CSI, compared to XRT CSI. This suggests that the thyroid and pituitary glands receive less radiation after spine and posterior fossa boost RT, respectively, using PRT.

## Introduction

Medulloblastoma is a malignant cerebellar tumor diagnosed in approximately 700–800 children and adolescents annually in the United States [1]. It requires a multimodal treatment approach that includes surgery, radiotherapy, and chemotherapy [2]. Advances in treatment over recent decades have led to significant improvements in survival, with five-year survival rates ranging between 60–85% depending on risk group at diagnosis, calculated by the extent of residual disease after surgery, age, and presence or absence of metastatic spread.

Though mortality has improved, curative therapy remains a significant source of long-term morbidity. Survivors of medulloblastoma are at risk for secondary malignancies, neurocognitive impairment, and many chronic medical conditions [3–5]. Craniospinal irradiation (CSI) often causes direct injury to the hypothalamic pituitary axis (HPA) and can, depending on the type of radiation and dose administered, also affect non-CNS organs including the thyroid gland, heart, lungs, liver, pancreas, kidneys, gonads, and bones including spinal growth [6]. Endocrinopathies are some of the most common adverse effects of CSI and include growth hormone deficiency (GHD), primary and secondary hypothyroidism, adrenal insufficiency (AI), hypogonadism, and precocious puberty [2, 7–11].

Improvements in the delivery of radiotherapy have resulted in enhanced coverage of the target organ and decreased irradiation to the normal surrounding structures. Recent studies comparing photon therapy (XRT) to proton therapy (PRT) have demonstrated that surrounding non-target organs, such as the HPA and the

thyroid gland, receive significantly less radiation with PRT than XRT [12–14]. Some have also reported a lower incidence of hypothyroidism and other late endocrine effects among patients treated with PRT [11, 15], highlighting the potential for newer technologies to result in fewer endocrine late effects. However, further research on the clinical effects of PRT relative to XRT is needed. In a recent analysis from our group, Bielamowicz et al reported a lower incidence of primary hypothyroidism among medulloblastoma patients treated with PRT compared to XRT; however, the difference did not reach statistical significance [15]. Here, we report on an expansion of this cohort with extended follow up time. In addition to reexamining hypothyroidism, this study compares rates of GHD and AI among patients treated with both XRT and PRT.

## Methods

### Patient Selection and Data Collection

We identified 127 patients diagnosed with medulloblastoma between 1997 and 2016 at Texas Children's Hospital. This observational medical record review was approved by the institutional review board at Baylor College of Medicine. Demographic variables, including age at diagnosis, gender, race and ethnicity, and clinical information, including diagnosis and treatment protocol, were abstracted from electronic medical records. All patients underwent maximal safe resection of the primary tumor followed by CSI, posterior fossa/tumor bed boost, and multi-agent chemotherapy. Before 2007, all patients were treated with 3D photons to the craniospinal axis followed by intensity-modulated radiation therapy (IMRT) for the boost volume. Almost all PRT patients received passive scatter proton therapy. Standard/low-risk patients received 15-23.4 Gy while high-risk patients received 36–39.6 Gy CSI. Cumulative radiation dose to the tumor bed ranged from 54 and 55.8 Gy. Two patients with incomplete radiation exposure information and two patients treated with both IMRT and PRT were excluded from the analysis. Five additional patients were also excluded because they were lost to follow up or did not have sufficient endocrinology evaluations to determine if a diagnosis was present or absent. The remaining 118 individuals were evaluable and included in the analysis.

### Endocrine Assessments

The primary endpoints for this study were incidence of hypothyroidism (primary or central hypothyroidism), GHD, and AI. After patients completed radiotherapy and chemotherapy, they continued regular follow up with oncology, long term survivor clinic, and/or endocrinology. Routine laboratory studies included thyroid stimulating hormone (TSH), free thyroxine (FT4), insulin-like growth factor-1 (IGF-1) and IGF binding protein-3. Total thyroxine (T4) and FT4 by equilibrium dialysis (FT4 by ED) were also utilized if available. If growth velocity or IGF-1 levels were suggestive of GHD, then growth hormone (GH) stimulation testing was often performed. Annual screening of cortisol function included evaluation for clinical symptoms suggestive of AI, and if clinically indicated, patients underwent 1 µg cosyntropin stimulation testing. In addition to the above studies, medication lists were reviewed to assess for hormone replacement therapy, and all notes from endocrine clinic visits were closely examined to ensure accurate diagnoses.

For the purposes of this study, primary hypothyroidism was defined as TSH > 10 mIU/L. Central hypothyroidism was defined as FT4 by ED lower than the normal range, FT4 < 80% of the lower limit of normal, or T4 < 80% of the lower limit of normal with normal or low TSH. Thyroid dysfunction not otherwise

specified (NOS) was defined as a clinical diagnosis without the appropriate supporting laboratory evidence available for analysis or lab criteria that do not fit one of the above diagnoses. Patients were excluded if they did not have thyroid studies at least one year from completion of chemotherapy. None of the patients included in the analysis had documentation of hypothyroidism prior to diagnosis.

GHD was defined as a peak human GH level during GH stimulation tests with two different stimuli of less than 10 ng/mL. Alternatively, if a patient did not have formal stimulation testing but had low IGF-1 levels with decreased growth velocity or was started on recombinant GH therapy by an endocrinologist, they were considered to have GHD. Patients were excluded from the GH analysis if they did not have a GH stimulation test, IGF-1 levels, or sufficient growth data for appropriate evaluation as the authors felt the diagnosis could be neither ruled in nor ruled out. Specific growth data reviewed included serial measurements of height and weight plotted on standard growth curves. Bone age was not assessed prior to radiation.

AI was defined as a peak cortisol level during a 1 µg cosyntropin stimulation test of less than 18 µg/dL. We also considered the relative diagnosis as supplied by a pediatric endocrinologist based on clinical data, which in some cases included patients who were empirically started on chronic hormone replacement therapy in the absence of formal stimulation testing.

We did not have sufficient data to assign a diagnosis of hypothyroidism, GHD, or AI in all patients. Patients were included in the analyses of a particular endocrine outcome when sufficient information was available for that endpoint, which resulted in slight differences in sample sizes between groups.

## Statistical Methods

The descriptive characteristics of the study sample were compared between radiation modalities (PRT and XRT) using standard methods (t-tests for continuous variables and Fisher's exact tests for categorical variables). Similarly, clinical and demographic characteristics of the cohort were compared between individuals with and without each endocrine outcome (hypothyroidism, AI, GHD). The cumulative incidence of each endocrinopathy was estimated with Kaplan-Meier method with follow up time defined from end of completion of RT until the date the individual developed a particular endocrinopathy or was censored at last follow up or 10-years post-radiotherapy, whichever came first. Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) comparing the incidence of each endocrine outcome between PRT and XRT. Associations between radiation modality and each endocrine outcome were adjusted for potential confounding variables, selected using a backwards stepwise approach to identify covariates associated ( $p < 0.2$ ) with at least one of the endocrine outcomes. Final models accounted for age, sex, and CSI radiation dose category. Secondary analyses further evaluated the associations between radiation modality and central or primary hypothyroidism. Patients with hypothyroidism NOS were excluded from this analysis. Finally, because temporal changes in the frequency of radiation modalities strongly correlated with treatment protocol, we performed a sensitivity analysis restricted to protocols (COG AA9961 and SJMB03) that included individuals treated with both XRT and PRT. Specifically, restricting the analysis to individuals treated according to these protocols, we calculated the probability of exposure to PRT (vs XRT) given the observed set of covariates (age, sex, diagnosis, CSI radiation dose category, and treatment protocol), and propensity score 1:1 matched PRT-treated to XRT-treated patients. Within the propensity-score

matched sample we evaluated with association between radiation modality and each endocrine outcome using Kaplan-Meier survival curves and log-rank p-values. All statistical comparisons were conducted applying a two-sided p-value < 0.05 to define statistical significance.

## Results

Patient clinical and demographic characteristics are presented in Table 1. Overall, 118 eligible patients were included in the analysis, consisting of mostly males (n = 85, 72%) of non-Hispanic white (n = 48, 40.7%) or Hispanic (n = 42, 35.6%) race/ethnicity. The mean age at diagnosis was 7.6 years (range: 2.0–18.0 years). The majority of patients were treated with < 30 Gy CSI (n = 80, 67.8%). As expected, compared to patients treated with XRT, those treated with PRT were more often treated during the more recent treatment era and according to more recent protocols (i.e., SJMB03, SJMB12) (p < 0.001).

Table 1

Clinical and demographic characteristics of patients with pediatric medulloblastoma, 1997–2016

	XRT (n = 54)	PRT (n = 64)	P-value
Mean age at diagnosis, year (SD)	8.47 (4.04)	6.83 (3.20)	0.02
Sex, n(%)	41 (75.9)	44 (68.8)	0.42
Male	13 (24.1)	20 (31.3)	
Female			
Race/Ethnicity, n(%)	19 (35.2)	29 (45.3)	0.37
Non-Hispanic White	19 (35.2)	23 (35.9)	
Hispanic	11 (20.4)	6 (9.4)	
Non-Hispanic Black	5 (9.3)	6 (9.4)	
Non-Hispanic Other			
CSI radiation dose, n(%)*	40 (74.1)	40 (63.5)	0.24
<30 Gy	14 (25.9)	23 (36.5)	
≥30 Gy			
Treatment Protocol, n(%)*	22 (40.7)	0 (0.0)	< 0.001
SJMB 96	15 (27.8)	38 (60.3)	
SJMB 03	14 (25.9)	7 (11.1)	
COG AA9961	0 (0.0)	9 (14.3)	
SJMB 12	3 (5.6)	9 (14.3)	
Other			

XRT, photon radiation therapy; PRT, proton radiation therapy; SD, standard deviation; CSI, craniospinal irradiation;

SJMB, St. Jude Medulloblastoma; COG, Children's Oncology Group

\*Data incomplete for CSI radiation dose (n = 1) and treatment protocol (n = 1).

	<b>XRT</b> <b>(n = 54)</b>	<b>PRT</b> <b>(n = 64)</b>	<b>P-value</b>
Diagnosis Year, n(%)	44 (81.5)	0 (0.0)	< 0.001
1997–2005	10 (18.5)	64 (100.0)	
2006–2016			
XRT, photon radiation therapy; PRT, proton radiation therapy; SD, standard deviation; CSI, craniospinal irradiation;			
SJMB, St. Jude Medulloblastoma; COG, Children’s Oncology Group			
*Data incomplete for CSI radiation dose (n = 1) and treatment protocol (n = 1).			

Patients were followed for a median of 5.6 years (range: 1.0–10.0 years) for the incidence of hypothyroidism, AI, and GHD. By five-years post-radiotherapy, the estimated cumulative incidence of hypothyroidism was 35.8% (95% CI: 26.7–47.1), compared to 15.9% for AI (95% CI: 9.8–25.3) and 63.2% for GHD (95% CI: 53.6–72.8) (Supplemental Fig. S1). The median time from end of radiotherapy to the development of each endocrinopathy among cases treated with PRT was: 2.1 years (range: 0.1–7.1 years) for hypothyroidism, 2.1 years (range: 0.1–7.1 years) for AI, and 2.4 years (range: 0.7–6.8 years) for GHD. For those treated with XRT, the median time to diagnosis of hypothyroidism, AI, and GHD was 2.9 years (range: 0.8–7.2 years), 3.9 years (range: 0.7–6.8 years), and 2.6 years (range: 1.4–9.6 years), respectively.

In univariate analyses, no clinical or demographic factors were associated with the prevalence of any endocrinopathy, with the exception of moderate differences in GHD across treatment protocols (Table 2). There was lower incidence of hypothyroidism, AI, and GHD among patients who received < 30 Gy compared to ≥ 30 Gy CSI, though none of these differences reached statistical significance.

Table 2

Association between clinical and demographic characteristics and endocrine outcomes in patients with pediatric medulloblastoma, 1997–2016

	Hypothyroidism			Adrenal Insufficiency			Growth Hormone Deficiency		
	Present (n = 35) *	Absent (n = 78) *	P-value	Present (n = 20) *	Absent (n = 94) *	P-value	Present (n = 71) *	Absent (n = 36) *	P-value
Mean age at diagnosis, yr (SD)	8.22 (4.29)	7.40 (3.54)	0.29	7.76 (3.82)	7.36 (3.58)	0.66	7.00 (3.17)	7.95 (4.18)	0.19
Sex, n(%)	24 (68.6)	56 (71.8)	0.82	17 (85.0)	65 (69.2)	0.17	51 (71.8)	26 (72.2)	0.96
Male									
Female	11 (31.4)	22 (28.2)		3 (15.0)	29 (30.9)		20 (28.2)	10 (27.8)	
Race/Ethnicity, n(%)	18 (51.4)	27 (34.6)	0.18	5 (25.0)	42 (44.7)	0.28	33 (46.5)	13 (36.1)	0.08
Non-Hispanic White	13 (37.1)	28 (35.9)		10 (50.0)	31 (33.0)		26 (36.6)	11 (30.6)	
Hispanic	3 (8.6)	14 (18.0)		4 (20.0)	12 (12.8)		8 (11.3)	5 (13.9)	
Non-Hispanic Black	1 (2.9)	9 (11.5)		1 (5.0)	9 (9.6)		4 (5.6)	7 (19.4)	
Non-Hispanic Other									
CSI radiation dose, n(%)	21 (60.0)	58 (74.4)	0.19	12 (60.0)	68 (72.3)	0.29	48 (67.6)	25 (71.4)	0.82
<30 Gy	14 (40.0)	20 (25.6)		8 (40.0)	26 (27.7)		23 (32.4)	10 (28.6)	
≥30 Gy									

\*Number of cases and controls may not combine to a total of 118 patients since patients were excluded if there was insufficient laboratory data to determine their endocrinopathy status.

SD, standard deviation; CSI, craniospinal irradiation; SJMB, St. Jude Medulloblastoma; COG, Children's Oncology Group

	Hypothyroidism			Adrenal Insufficiency			Growth Hormone Deficiency		
Treatment Protocol, n(%)	7 (20.0)	14 (18.0)	0.35	2 (10.0)	20 (21.3)	0.30	11 (15.5)	4 (11.4)	0.04
SJMB 96	17 (48.6)	35 (44.9)		9 (45.0)	43 (45.7)		37 (52.1)	14 (40.0)	
SJMB 03									
COG AA9961	8 (22.9)	13 (16.7)		7 (35.0)	14 (14.9)		14 (19.7)	5 (14.3)	
SJMB 12	0 (0.0)	8 (10.3)		1 (5.0)	7 (7.5)		6 (8.5)	3 (8.6)	
Other	3 (8.6)	8 (10.3)		1 (5.0)	10 (10.6)		3 (4.2)	9 (25.7)	
*Number of cases and controls may not combine to a total of 118 patients since patients were excluded if there was insufficient laboratory data to determine their endocrinopathy status.									
SD, standard deviation; CSI, craniospinal irradiation; SJMB, St. Jude Medulloblastoma; COG, Children's Oncology Group									

Multivariable Cox proportional hazards models were used to assess the association between radiation modality and each endocrine outcome while accounting for age at diagnosis, sex, and CSI radiation dose (Table 3). Compared to patients receiving PRT, patients receiving XRT had higher rates of hypothyroidism (HR = 2.36, 95% CI: 1.11–5.02). Differences in hypothyroidism risk by radiation modality were largely attributed to higher rates of primary hypothyroidism following XRT (HR = 4.61, 95% CI: 1.20-17.66). The difference in the incidence of central hypothyroidism between PRT and XRT did not achieve statistical significance (HR = 2.35, 95% CI: 0.81–6.82). The rates of AI (HR = 1.07, 95% CI: 0.41–2.81) and GHD (HR = 0.71, 95% CI: 0.43–1.17) were similar between the two radiation groups (Table 4).

Table 3  
Adjusted associations between cranial radiotherapy modality and incidence of endocrine outcomes

	Events	Total	HR (95% CI)
Endocrine outcome	10	60	Ref.
Any hypothyroidism	25	53	2.36 (1.11–5.02)
PRT	5*	55	Ref.
XRT	14	42	2.35 (0.81–6.82)
Central hypothyroidism	3*	53	Ref.
PRT	11	39	4.61 (1.20-17.66)
XRT	8	60	Ref.
Primary hypothyroidism	12	54	1.07 (0.41–2.81)
PRT	39	62	Ref.
XRT	22	45	0.71 (0.43–1.17)
Adrenal insufficiency			
PRT			
XRT			
Growth hormone deficiency			
PRT			
XRT			
Adjusted for age at diagnosis, sex, race/ethnicity, and CSI radiation dose			
*The sum of central and primary hypothyroidism events does not combine to equal the hypothyroidism events as two patients receiving PRT were diagnosed with hypothyroidism not otherwise specified (NOS).			
HR, hazard ratio; CI, confidence interval; XRT, photon radiation therapy; PRT, proton radiation therapy			

In order to evaluate whether differences in endocrinopathies could be attributed to temporal or protocol-specific differences detection, we conducted a propensity score-matched comparison restricted to patients treated on AA9961 and SJMB03 (Supplemental Fig. S2). The propensity score-matched sensitivity analysis

resulted in similar findings as the overall analysis, indicating an association between PRT with lower incidence of hypothyroidism and similar rates of AI and GHD for the two radiation modalities. These results suggest variation in chemotherapy and/or temporal changes in the screening of endocrine function are unlikely to explain the observed benefits of PRT.

## Discussion

Treatment of pediatric brain tumors is an evolving field. With improvements in mortality, more attention has been focused on maximizing quality of life (QOL) and minimizing effects of therapy. There are efforts to tailor treatment protocols and reduce radiation doses in patients with more favorable molecular subtypes [16]. Advances in radiation therapy, including PRT, promise to reduce radiation doses delivered to normal tissues. Data is needed to further evaluate whether PRT is superior to XRT in terms of reducing clinically meaningful long-term sequelae of radiation and whether dose reductions can achieve similar survival rates.

Two prior studies done by Eaton et al. and Bielamowicz et al. directly examined the differences between PRT and XRT [11, 15]. Eaton et al. found that PRT was associated with lower incidence of hypothyroidism and sex hormone deficiency, reduced need for endocrine replacement therapy, and greater height SDS at follow up. Bielamowicz et al. focused on hypothyroidism, specifically looking at central and primary hypothyroidism, and while not statistically significant, the data suggested a trend towards decreased risk of both primary and central hypothyroidism.

This study extends the work of Bielamowicz et al. to examine the incidence of primary and central hypothyroidism, GHD, and AI at a single institution among patients who have undergone both PRT and XRT. There was a higher incidence of hypothyroidism among patients who underwent XRT even after accounting for age at diagnosis, sex, race/ethnicity, and CSI radiation dose. More specifically there was higher incidence of primary and central hypothyroidism among XRT vs. PRT patients. Difference in the incidence of primary hypothyroidism supports prior hypotheses that spinal RT using protons may spare normal healthy tissues such as the thyroid, heart, and lungs that are distant from the target volume. Difference in the incidence of central hypothyroidism, while statistically insignificant, should cautiously be noted. This suggests that pituitary gland may have less radiation exposure after posterior fossa boost in patients treated with PRT CSI compared to XRT CSI. There was no significant difference between the incidences of AI or GHD between the two groups. Thus, the overall risk of HPA dysfunction remains similar despite use of PRT, and shows that the relative sensitivity of the growth hormone and ACTH producing pituitary tissue to RT is high even with lower overall dosage. This is consistent with the study done by Merchant et al., which suggested that the dose to the HPA was large enough with both PRT and XRT to cause GHD [17].

While there remained lower rates of hypothyroidism with PRT compared to XRT due to the difference in targeted dosage to the thyroid gland, the length of follow up was unable to ascertain the potential difference in outcomes of secondary thyroid cancer progression. Thyroid cancer is a known complication of spinal RT following medulloblastoma due to mutational transformation of the surviving thyroid tissue following irradiation [20]. XRT therapy for medulloblastoma was previously shown to have an 18 fold increase in observed to expected case ratio in thyroid cancer incidence, typically occurring at more than 5–10 years from exposure [21]. A concern however is that at higher targeted doses to the thyroid of > 2 Gy, the relative

incidence of thyroid cancer is flat due to higher rate of cell destruction within the thyroid gland, while at lower doses between 0.2-2 Gy, there is a linear increase in the rate of thyroid cancer [22, 23]. This effect is caused by lower rates of cell destruction and sterilization of thyroid tissue at lower doses of RT but predisposing those tissues to malignant transformation. While lower overall doses of thyroid targeted RT with PRT may allow for reduced thyroid hormonal dysfunction, theoretically this actually may increase the overall incidence of secondary thyroid cancer. Although prior models have suggested a lower overall projected incidence of all cause secondary cancers with PRT vs. XRT among medulloblastoma survivors, the true rate of secondary thyroid cancer with PRT in this population is unknown and deserves long term follow up studies to determine outcomes [24].

This single-site, retrospective cohort study evaluated a large cohort of pediatric patients with medulloblastoma, where follow up laboratory studies and endocrinology referrals have become more standardized. The criteria used to diagnose hypothyroidism, were strictly defined, similar to the study done by Bielamowicz et al., and did not include cases of subclinical hypothyroidism unless started on thyroid replacement therapy. With PRT now in use at our institution for over ten years, there are patients who have had significant follow up time to allow for the development of endocrine sequelae. Prior studies have shown that the majority of endocrinopathies may occur in the subsequent 6 years from tumor therapy [33, 34], but endocrine complications have been reported decades later [35, 36], so re-assessing this cohort in the future may still be beneficial and may clarify what impact, if any, length time bias has on these outcomes. While this study's median follow up was 5.6 years and likely reports a majority of outcomes for those individuals with > 5 years of follow up, it is possible that for patients with follow up time < 5 years and particularly < 2 years (all patients treated with PRT), the incidence of endocrine dysfunction may be underreported [17, 18, 37].

A limitation of this study was that some patients that had received XRT were not included in the analysis due to lack of timely and regular endocrine testing in the early 2000s. An additional limitation relates to the stimulation testing for GHD and AI. In most situations, stimulation testing was only performed if clinically indicated (obvious abnormalities in growth patterns, abnormal IGF testing, abnormal cortisol testing or symptoms of AI), which could explain lower incidence of GHD in our study. However, in later years more standardized referral to endocrinology and serial testing was adopted, and thus closer monitoring of endocrine function may have improved the findings in this study. In fact, rates of AI in our study were higher than the published literature, which could be related to more proactive screening protocols in recent years.

Ultimately, the results of this study add to the evidence that PRT results in less harm to non-target organs such as the thyroid and possibly the pituitary gland, leading to improved endocrine outcomes. Specifically in our study, there is a decreased risk of any hypothyroidism overall, and primary hypothyroidism in particular, with PRT in comparison to XRT. We observed similar rates of GHD and AI with PRT and XRT. However, further studies are needed to investigate longer-term effects of PRT and verify whether this finding remains statistically significant in a cohort followed decades after completion of therapy. Further studies must also be performed to assess whether lower radiation doses achieved with PRT will impact the rate of thyroid malignancy and reduce the risk of late effects on the heart and lungs.

## Declarations

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**Conflict of Interest:** The authors have no conflicts of interest to disclose. The authors have no relevant financial or non-financial interests to disclose.

**Ethics approval:** The study procedures were reviewed and approved by an Institutional Review Board at Baylor College of Medicine.

**Consent to participate:** Informed consent was not required for this retrospective chart abstraction.

**Availability of data and material:** All data was obtained upon retrospective review from patient medical records and is not publicly available. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Code availability:** not applicable

**Authors' contribution:** All authors contributed to the study conception and design. Material preparation and data collection were performed by K. Danielle Aldrich, Vincent Horne, and Kevin Bielamowicz. Austin Brown performed the formal analysis. The first draft of the manuscript was written by K. Danielle Aldrich and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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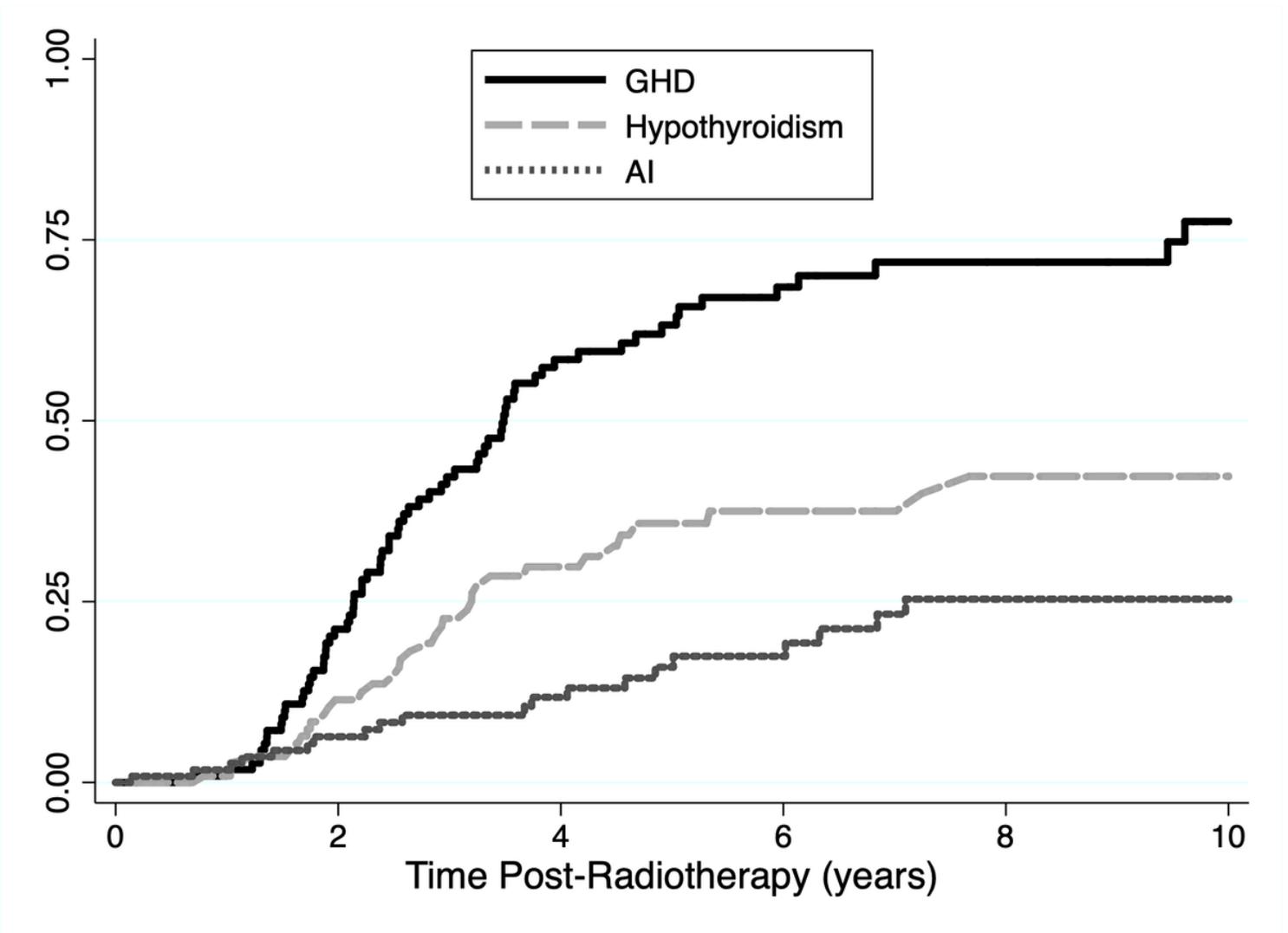
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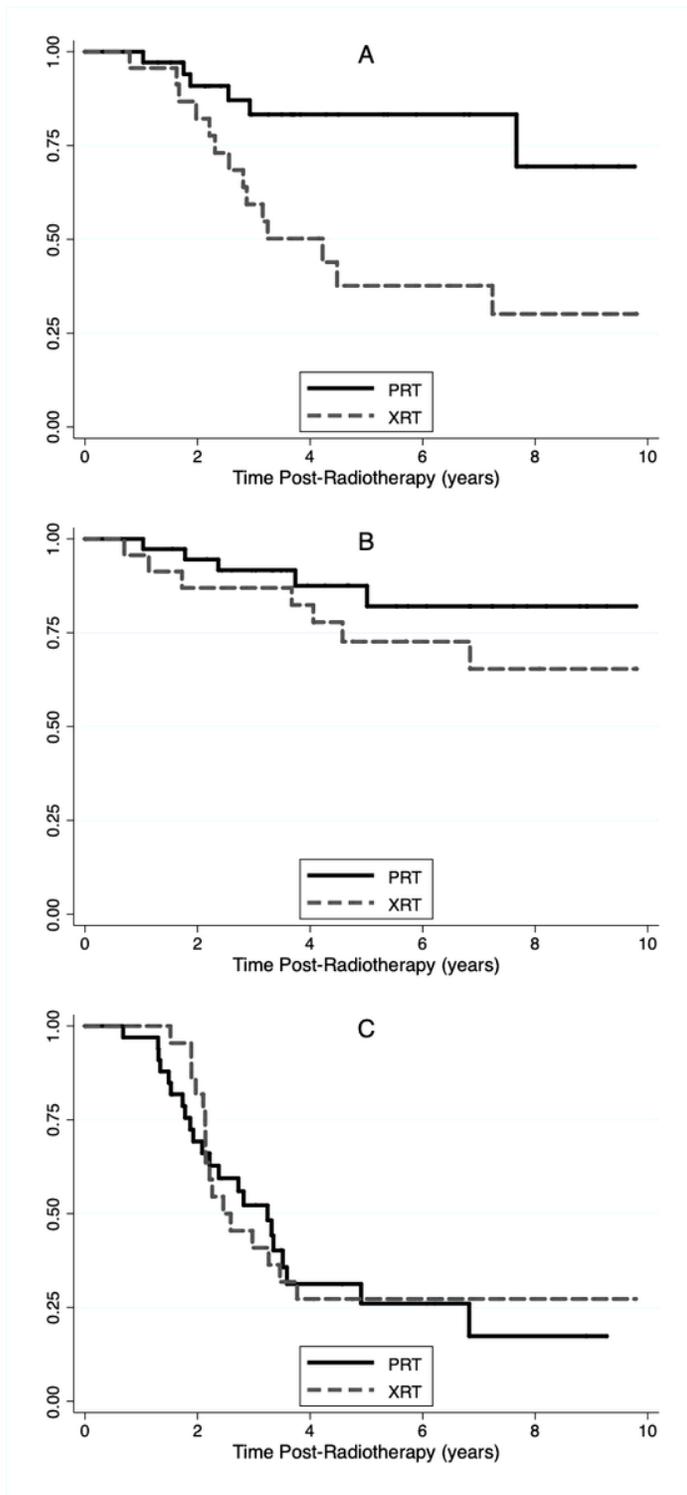
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## Figures



**Figure 1**

Kaplan-Meier cumulative incidence plots from hypothyroidism, adrenal insufficiency, and growth hormone deficiency



**Figure 2**

Kaplan-Meier plots comparing incidence of hypothyroidism (A,  $p=0.006$ ), adrenal insufficiency (B,  $p=0.62$ ), and growth hormone deficiency (C,  $p=0.61$ ) between XRT and PRT, propensity-score matched on age at diagnosis, sex, CSI radiation dose, and treatment protocol (COG AA9961 or SJMB03)