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Scholarly Report submitted in partial fulfillment of the MD Degree at Harvard Medical School

Date: 1 February 2016

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Scholarly Report Title: The effect of proton radiation therapy on thyroid function in the treatment of pediatric medulloblastoma

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TITLE: The effect of proton radiation therapy on thyroid function in the treatment of pediatric medulloblastoma.

Eli J. Muhrer, Laurie E. Cohen

Purpose: To investigate the development of hypothyroidism in this population over time and its relationship to the amount of scatter dose to the thyroid, pituitary, and hypothalamus.

Methods: A retrospective chart review of patients diagnosed with medulloblastoma between the years 2003 and 2010 at Dana Farber-Cancer Institute/Boston Children's Hospital. Subjects included in the analysis received both CSI and radiation therapy (RT) boost to the tumor by proton therapy. Patients were classified as being euthyroid or having primary, compensated, or central hypothyroidism.

Results: 24 fit criteria for analysis. Incidence of hypothyroidism of all forms was 8/24 (33%). There were no cases of primary hypothyroidism. The incidence of compensated hypothyroidism was 5/24 (21%) and of central hypothyroidism was 3/24 (12.5%). For compensated hypothyroidism, mean time to diagnosis from initiation of RT was 2.30 years (range 1.44 to 3.38). Comparing compensated hypothyroidism *vs.* euthyroidism, mean age at initiation of RT, 5% thyroid dose, 50% thyroid dose, 90% thyroid dose, and CSI dose were not significant. Mean pituitary dosing was significantly higher in those with central hypothyroidism versus all other patients ($p=0.0001$)

Conclusions: Despite minimal radiation to the thyroid gland, hypothyroidism is a sequelae in pediatric patients with medulloblastoma who receive proton RT. The current analysis shows no predictor of who develops compensated hypothyroidism (thyroid injury). Higher dose pituitary radiation was associated with increased central hypothyroidism, which could have masked primary or compensated hypothyroidism.

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Glossary of abbreviations

RT: Radiation therapy; CSI: craniospinal radiation; TSH: thyroid stimulating hormone; T4: thyroxine; MGH: Massachusetts General Hospital; DFCI: Dana-Farber Cancer Institute; BCH: Boston Children's Hospital; Gy: gray.

Section 1: Introduction

Due to recent advancements in cancer treatments, the overall 5-year cure rate for pediatric central nervous system tumors is 67%[1], and the overall 5-year cure rate for medulloblastoma is 85%[2]. With this increase in survival, it is important to recognize and treat the long-term sequelae of cancer therapy. Of these sequelae, endocrine disturbances have been documented in 20% to 50% of childhood cancer survivors[3]. In one recent study, 48% of females and 62% of males were affected by at least one endocrine disease at median length of follow-up of 16.09 years[4]. Endocrine disturbances are especially of concern in the treatment of pediatric brain tumors due to the use of radiation therapy (RT).

Radiation therapy for medulloblastoma is delivered by external beam radiation with photons or protons. Photons (x-rays),are the source of energy for conventional RT. Photons deposit energy along their path and while the highest dose is at the target site, there is exposure of surrounding tissues. Protons are bundles of energy created via a particle accelerator. Unlike photons, the protons deliver most of their energy at the target while minimizing exposure of surrounding tissues. Thus, the function of the surrounding normal tissue can theoretically be conserved, and it may be possible to use higher doses of radiation to tumors than for photon beam therapy[5]. Since proton RT has only been used in the United States in a select few locations since the early 2000s, its long-term effects have yet to be fully understood[6].

Given the sensitivity of the thyroid to radiation and the increasing survival of children with a history of brain tumors, it is increasingly important to follow their thyroid function. Since hypothyroidism can present in many forms, including compensated (subclinical hypothyroidism), it is important to characterize its incidence. Thyroid hormone is critical for children's growth and development, including that of the brain up until 3 years of age[7]. For these reasons, assessing the dose the thyroid receives in proton therapy, which is purported to be safe for the thyroid, and its impact on thyroid function over time is essential to taking better care of the growing population of pediatric cancer survivors. Finally, although it is beyond the scope of this study, it is important to follow the development of thyroid nodules and neoplasms, since the radiation can lead to this outcome as well, although this takes place over more years than allotted for this study.

Medulloblastoma is the most common malignant primary brain tumor in children and accounts for approximately 20% of all pediatric central nervous system malignancies[8]. It is located in the cerebellum, most typically in the midline of the inferior vermis[9]. Craniospinal radiation (CSI) with an additional boost to the primary tumor, along with chemotherapy, is currently the most effective treatment post-surgical resection. Typically, CSI is delivered to the entire craniospinal axis because the spine and cerebrospinal

fluid are considered potential reservoirs of tumor cells, even if not clinically detectable. The craniospinal dose is typically 23.4 Gy for standard risk and 36 Gy for high risk tumors, with a local boost of radiation to the primary tumor site to 55.8 Gy[10]. Historically, treatment has been with photon therapy. However, more recently, proton radiation has been used to target the tumor while trying to minimize damage to healthy surrounding tissue. Despite this specificity, scatter doses to surrounding tissue can occur (Figure 1).

The thyroid gland is especially sensitive to radiation with thyroid-ablative radiation doses ranging between 10 to 80 Gy[11]. Hypothyroidism, both the primary type as defined by a low thyroxine (T4) level and an elevated thyrotropin (TSH) level and the compensated type as defined by a normal T4 level and an elevated TSH level, is the most common thyroid disturbance after thyroid gland irradiation with photon radiation.

The onset of the hypothyroidism increases with increasing doses of radiation and although a threshold is not known, doses as low as 7.5 Gy have been associated with hypothyroidism, specifically primary and compensated forms[12]. In patients with medulloblastoma receiving photon radiation, it was that found that only 1 of 7 patients who received 18 Gy developed primary hypothyroidism compared with 10 of 12 patients who received 23 to 39 Gy despite being treated with identical chemotherapy and having identical tumor stage.[13] Little is known about the effect proton RT has on the thyroid, that is, whether it delivers a thyroid scatter dose significant enough to the thyroid gland to cause problems. Additionally, the incidence of central hypothyroidism due to injury to the hypothalamus and/or pituitary after RT for pediatric brain tumors, as diagnosed by a low T4 concentration with an inappropriately normal TSH level, was 6% in one study but has been reported to be as high as 80% in other studies[14,15,16,17].

Given the sensitivity of the thyroid to radiation and the increasing survival rates of children with a brain cancer, it is imperative to recognize the endocrine deficiencies this population is facing due to treatment. Review of the literature reveals one study to date that compares the development of hypothyroidism in pediatric patients with medulloblastoma between those receiving proton versus photon RT[18]. This study found that proton therapy was associated with a reduced risk of hypothyroidism (23% vs. 78%, p=0.030) but no significant difference in the incidence of growth hormone deficiency (53% vs. 57%), adrenal insufficiency (5% vs. 8%), or precocious puberty (18% vs. 16%), which are all due to hypothalamic-pituitary injury, areas that received the same total dose of radiation due to the whole brain component. Thus, proton radiation may reduce the risk of some, but not all, radiation associated late endocrine abnormalities.

To date, no other study has tracked hypothyroidism and its relationship to scatter dose from proton RT longitudinally in the pediatric medulloblastoma population. The goal of this study was to therefore calculate both the scatter dose and the highest RT dose delivered to the thyroid gland to see if there was a correlation between RT dose and thyroid injury. We also determined what doses various percentages of the thyroid received.. Although a retrospective study, laboratory data were collected longitudinally after CSI, which allowed us to assess the timeline of thyroid disturbance as it can develop slowly and over months to years. Further, studies have not correlated incidence of hypothyroidism with specific doses of proton beam therapy in this population. For these reasons, this study addressed critical gaps in the literature.

Although it has been argued that the thyroid does not receive significant enough levels of radiation from proton RT to cause damage, based on clinician reports, we hypothesized that the thyroid receives scatter doses high enough to cause thyroid toxicity. Further, we predicted that the toxicity will manifest as compensated primary hypothyroidism where T4 is normal but TSH is mildly elevated. We expected the incidence of hypothyroidism would increase as the length of follow-up time from CSI increases.

Section 2: Student Role

My specific role involved completing the collection of the data, organizing and analyzing the dataset, and working towards a publication. I worked within an interdisciplinary team, including pediatric endocrinologists, pediatric oncologists, and radiation oncologists to collect, analyze and write-up the data.

Section 3: Methods

Patient Selection:

A retrospective chart review was conducted of patients diagnosed with medulloblastoma between the years 2003 (the first year proton therapy was utilized for this cohort) and 2010 at Dana Farber-Cancer Institute (DFCI)/Boston Children's Hospital (BCH) treated with proton radiation at Massachusetts General Hospital (MGH). 37 patients were identified. Five patients were excluded because they received CSI by photon radiation, 6 were excluded because they were started on levothyroxine without meeting the study criteria for hypothyroidism, and 2 were excluded because there were no thyroid function data, leaving 24 patients available for analysis. CSI dose administered was determined based on initial risk assessment, either 24 Gy [standard risk (SR)] or 36 Gy [high risk (HR)]. The Radiation Oncology Program at MGH provided scatter radiation doses —the dose to 90%, 50%, and 5% of the thyroid gland; as well as the dose to 50% of the hypothalamus and to 50% of the pituitary gland.

Thyroid function data were collected from the Endocrinology and Neuro-oncology follow-up visits at BCH and DFCI, respectively. Hypothyroidism was defined as primary if the thyroid hormone level was low and the TSH level was elevated, compensated if the thyroid hormone level was within normal range and the TSH level was elevated, and central if the thyroid hormone level was low and the TSH level was low or inappropriately normal. A TSH level was considered elevated if >10 uIU/mL on one occasion or two TSH levels above normal range and <10 uIU/mL separated by at least 3 months.

Outcome Variables and Assessments

Primary outcome: Incidence of thyroid injury as defined by TSH elevation.

Secondary outcomes: Associations with TSH elevation, including dose of radiation to the thyroid, dose of radiation to the hypothalamic-pituitary axis, time from treatment with radiation, age, and sex.

Data Analysis:

Because of the small sample size, two-tailed, unpaired T-tests were used to compare individual variables with the development of hypothyroidism vs. remaining euthyroid. Variables included mean age at initiation of RT, thyroid doses 5%, 50%, and 90%, hypothalamic dose, and pituitary dose. Chi-square tests were used to compare these groups based on whether they received a CSI dose of 23.4 Gy or 36 Gy and for gender. Groups included euthyroid, compensated hypothyroidism, and central hypothyroidism.

Section 4: Results

Patient Population:

Of the 24 patients included in the primary analysis, mean age at diagnosis of medulloblastoma was 5.6 years (range 3.4-14.6). There were 11 females (46%) and 13 males (54%), *P=NS*. Of the 22 patients with CSI dose information, 15 received low-dose CSI of 23.4 Gy, while 7 received high-dose CSI of 36 Gy (see Table 1). Two patients (8%) experienced recurrence of medulloblastoma. All received chemotherapy.

Incidence of Hypothyroidism (Table 1)

Incidence of hypothyroidism of all forms was 8/24 (33%). There were no cases of primary hypothyroidism. The incidence of compensated hypothyroidism was 5/24 (21%) and of central hypothyroidism 3/24 (12.5%). Mean age at time of any hypothyroidism diagnosis was 8.99 years (range 5.30 to 11.78), and mean time to diagnosis from initiation of RT was 2.73 years (range 1.65 to 4.24). For compensated hypothyroidism, specifically, mean age at the time of diagnosis was 8.40 years (range 5.30 to 11.02), and mean time to diagnosis from initiation of RT was 2.30 years (range 1.44 to 3.38).

Comparing compensated hypothyroidism *vs.* euthyroidism, mean age at initiation of radiation therapy, 5% thyroid dose, 50% thyroid dose, 90% thyroid dose, mean hypothalamic dose, mean pituitary dose, and CSI dose were not significantly different between patients with compensated hypothyroidism and all other patients. (see Table 2).

Mean pituitary dosing was significantly higher in those with central hypothyroidism versus all other patients (p=0.0001) with a mean dose of 44.3 Gy in central hypothyroid patients versus 26.6 Gy in all other patients. There was no significant difference between hypothalamic dosing. Age at initiation of radiation was not significant.

Section 5: Discussion, Limitations, Conclusion, and Future Directions

Patients who received proton RT developed hypothyroidism one third of the time. Of those who developed hypothyroidism, none developed primary, 21% developed compensated, and 12.5% developed central hypothyroidism. Our patients are a subgroup of a cohort previously described by Eaton *et al*, who found an incidence of 23% of hypothyroidism in those patients treated with proton RT, but did not describe type of hypothyroidism or any variables associated with it, other than CSI dose.[17] In constrast, a study by MacDonald *et al* in pediatric patients receiving local proton RT for ependymoma but no CSI found a rate of only 1/32 (3%) cases of hypothyroidism, which was a case of central hypothyroidism.[19] Taken together, these two studies suggest that proton spinal RT, but not cranial RT, is associated with thyroid injury.

Although the rate of hypothyroidism is significantly less than that of patients who received photon therapy (ranging from 15-80% in studies) compared to proton therapy (23% vs. 69% in Eaton et al.'s direct comparison), this incidence is not trivial.[17] Moreover, hypothyroidism was likely under-diagnosed in our cohort as patients with incomplete data were considered to have normal thyroid function and cranial radiation may blunt hypothalamic-pituitary function causing a falsely normal TSH. Longer follow-up in larger populations may reveal even higher rates of hypothyroidism, especially given that proton radiation therapy was introduced relatively recently compared to photon therapy.

The decreased incidence of hypothyroidism in proton versus photon patients is, at least in part, due to reduced scatter. To better characterize the scatter doses in proton therapy, this study analyzed what 5%, 50%, and 90% of the thyroid received. Additionally, scatter dose to 50% of the pituitary and hypothalamus were determined (see Figure 2). For the first time in the literature, scatter doses were compared between euthyroid and hypothyroid patients. These analyses did not reveal a significant difference in scatter dose to the thyroid between compensated hypothyroidism and euthyroid patients,

which may have been due to small sample size or may suggest that there is no radiation threshold and other factors modify the develop of hypothyroidism. Of note, there was a significant difference in pituitary dosing between those who developed central hypothyroidism *vs.* all other patients. Interestingly, there was not a significant difference in hypothalamic dosing. It is possible, however, that smaller, more focal areas of the hypothalamus received higher doses since this study did not include what 5% of the hypothalamus received. Further quantifying scatter doses in this way will be critical to understanding which patients develop central hypothyroidism.

The greatest limitation of this study is the sample size. Although this study was the first to integrate scatter dose into the comparison between hypothyroidism and euthyroid patients, it was underpowered, and larger studies may show an association between radiation dosing and development of compensated hypothyroidism. There was patient attrition as a result of loss to follow-up or tumor recurrence. Since since this is a retrospective study of clinical care, the screening for patients' thyroid function was not consistent; it instead relied on the clinicians' discretion, and several patients were excluded because they were started on levothyroxine despite not meeting the research criteria for hypothyroidism. Additionally, as patients follow-up appointments were variable and providers changed, data for all time points were not obtainable. The hypothalamic-pituitary axis (HPA) received radiation in the field and thus compensated primary hypothyroidism may have been masked by a blunted HPA. Most importantly, the relatively short median follow-up time may have been insufficient for hypothyroidism to develop.

Despite the limitations of this study, it is the first in the literature to not only report the incidence of hypothyroidism in pediatric medulloblastoma patients after proton RT, but also to correlate that to the scatter doses to the thyroid, hypothalamus, and pituitary. An important finding is that low doses of radiation to only a small area of the thyroid may cause enough injury to cause thyroid dysfunction. Studies like this are critical to understand the long-term effects of recent advancements in cancer treatments, such as proton RT. Additionally, these therapies have led to patients with cancer surviving significantly longer, allowing sequelae to develop. Endocrine disturbances, such as hypothyroidism, are especially of concern in the treatment of pediatric brain tumors.

Future studies are needed to further understand what predicts which patients develop hypothyroidism. Although this study followed patients for several years, future prospective studies are needed to track larger cohorts of patients systematically for longer periods of time. Those studies will enable us to determine if proton radiation truly leads to a lower incidence of hypothyroidism, or whether it just develops earlier after photon therapy.

Section 6: Acknowledgements

Laurie Cohen, MD was instrumental in the collection, analysis, and write-up of this study. The data collection would not have been possible without the help of Jessica Smith, MD (Endocrinology, BCH). Peter Manley, MD provided details of the cancer therapy. Hallie Kasper, NP and Torunn Yock, MD provided the radiation data. Henry Feldman provide advice on statistical analysis.

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Tables and Figures:

Figure 1: Example of dosimetry analysis for various tissues in one patient. The arrow indicates dosimetry to the thyroid gland.

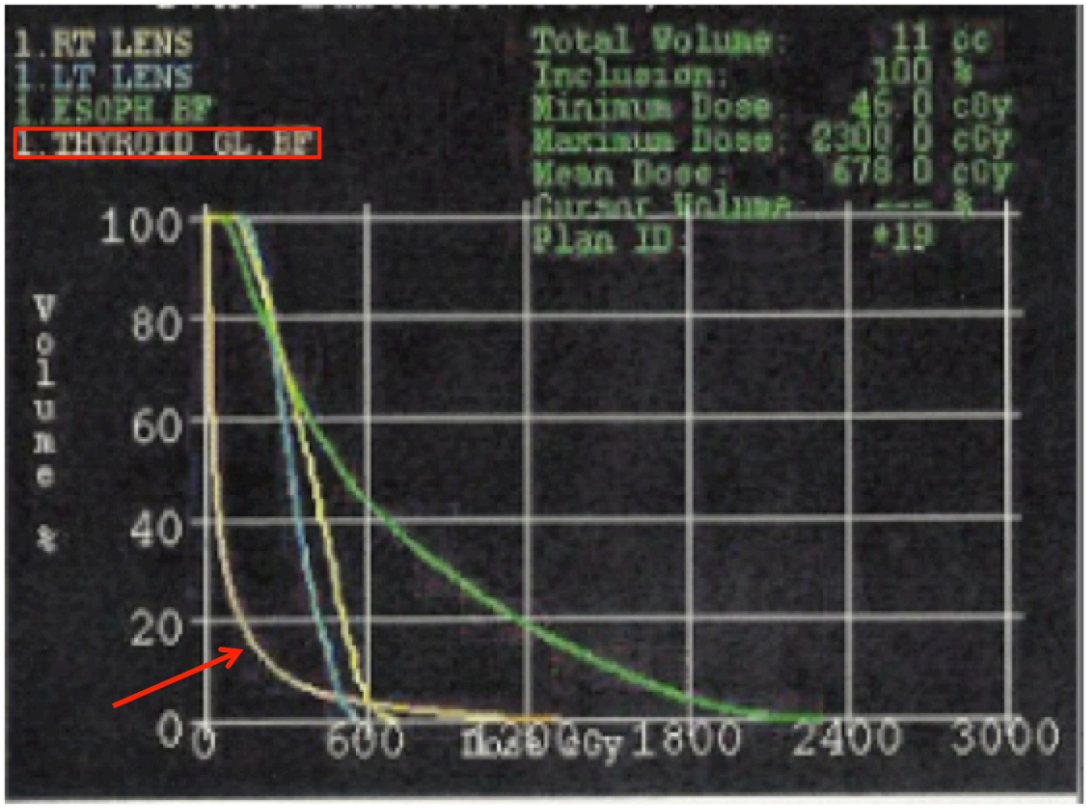

Table 1: Patient Characteristics

Number of Patients	24
Gender Male (%) Female (%)	 13 (54) 11 (46
Medulloblastoma risk High risk (%) Standard risk (%)	 7 (32) 15 (68)
Median age at diagnosis of medulloblastoma in years (range)	5.63 (3.42 to 14.63)
Median age at initiation of radiation therapy in years (range)	5.63 (3.42 to 14.63)
Median length of follow-up in years (range)	5.1 (1.31 to 6.89)
Hypothyroidism Euthyroid (%) Central hypothyroidism (%) Compensated hypothyroidism (%)	 16 (67) 3 (12.5) 5 (21)

Table 2: Development of Compensated Hypothyroidism

	Euthyroid	Compensated Hypothyroidism	P-value
Number of Patients	16	5	N/A
Gender Male (%) Female (%)	 9 (56) 7 (44)	 1 (20) 4 (80)	p=0.16
Median follow-up time either to diagnosis of hypothyroidism, or to last thyroid laboratory study in years	5.06	1.88	p=.06
Median age at diagnosis of hypothyroidism in years (range)	N/A	8.40	N/A
Median age at diagnosis of medulloblastoma in years (range)	5.41	6.95	p=0.54
Median age at initiation of radiation therapy in years (range)	5.42	6.96	p=0.55

Table 3: Proton radiation scatter doses by thyroid function and region

Location %	Euthyroid: scatter dose median (range) Gy	Central hypothyroidism: Scatter dose median (range) Gy	Compensated Hypothyroidism: scatter dose median (range) Gy	P value for compensated vs. euthyroid
Thyroid 5	2.34 (0.27 to 12.79)	0.62 (0.4 to 0.83)	2.29 (0.4 to 6.14)	p=0.98
Thyroid 50	0.32 (0 to 1.47)	1.37 (0.1 to 3.5)	0.31 (0.04 to 1.06)	p=0.94
Thyroid 90	0.22 (0 to 1.4)	0.02 (0.02 to 0.02)	0.05 (0 to 0.2)	p=0.44
Pituitary 50	26.62 (19.6 to 43.9)	44.30 (38.1 to 52.7)	26.68 (23.5 to 29.4)	p=0.99
Hypothalamus 50	33.59 (21.7 to 49.5)	42.87 (40.1 to 42.3)	31.55 (23.7 to 43.3)	p=0.71