LATE EFFECTS OF HYPOTHALAMIC RADIATION EXPOSURE IN PEDIATRIC BRAIN TUMOR SURVIVORS

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by

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DISSERTATION

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ABSTRACT

LATE EFFECTS OF HYPOTHALAMIC RADIATION EXPOSURE IN PEDIATRIC BRAIN TUMOR SURVIVORS

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Background: Brain tumors are the second most common childhood malignancy and overall survival rates exceed 70%. Pediatric brain tumor survivors treated with hypothalamic radiation are at increased risk for developing components of metabolic syndrome, characterized by central obesity and two of the following: elevated triglycerides, low HDL, elevated blood pressure, or fasting hyperglycemia. These patients may also be at risk for developing decreased bone density, which is associated with pathologic fractures.

Objective: Our aim is to compare the prevalence of metabolic syndrome or concomitant cardiometabolic risk, bone density, and body composition among pediatric brain tumor survivors treated with and without hypothalamic radiation.

Methods: This study evaluated 146 survivors of childhood brain tumors (70 radiated, 76 non-radiated) between 5-20 years old (mean: 12.3 years, SD: 4.1 years, average survival time: 6 years). Patients underwent fasting lab assays (lipid panel, insulin, glucose, leptin, and adiponectin), anthropometric measurements (height, weight, and waist circumference), and Dual-energy X-ray Absorptiometry (DXA) scan. Insulin resistance was identified using the homeostasis model assessment of insulin resistance (HOMA-IR). Metabolic syndrome was diagnosed according to the International Diabetes Foundation criteria in children 10 years and older; children between 5-10 years of age who met 3 of 5 risk factors were classified as having concomitant cardiometabolic risk.

Results: Metabolic syndrome or concomitant cardiometabolic risk was more common in patients who received hypothalamic-pituitary axis (HPA) radiation (7/38, 18.4%) than those who did not (4/76, 5.3%) ($p = 0.04$). Patients who received HPA radiation were more likely to have elevated triglyceride levels ($p = 0.02$), low HDL levels ($p = 0.04$), and lower IGF-1 z-scores ($p < 0.001$). On DXA scan, patients exposed to HPA radiation had lower Bone Mineral Content (BMC) and Bone Mineral Density (BMD) z-scores (-1.3 vs. -0.3, $p = 0.003$ and -1.4 vs. -0.2, $p < 0.001$ respectively) and lower Fat Free Mass Index z-scores (-1.4 vs. -0.1, $p = 0.001$) despite no significant difference in BMI (21.7 vs. 22.2, $p = 0.7$) or percent body fat (35.5% vs. 32.8%, $p = 0.11$). There was no significant difference in leptin/kg fat and adiponectin/kg fat between patients who received HPA radiation and those who did not ($p = 0.55$ and $p = 0.98$ respectively). Patients with elevated HOMA-IR had elevated leptin levels ($p = 0.001$), lower adiponectin levels ($p = 0.04$), and elevated leptin:adiponectin ratios ($p = 0.001$).

Conclusion: These results suggest that exposure to hypothalamic radiation may have significant subclinical consequences that include components of metabolic syndrome, decreased bone density, and altered body composition. These results highlight the need for stringent follow-up surveillance of these patients and suggest that screening for dyslipidemia may be a sensitive way to detect patients at risk for developing metabolic syndrome.

PRIOR PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS:
None

PRESENTATIONS AND POSTERS:

Susan Y. Wu, Raven Cooksey, Amit Gode, Laura Klesse, Jon Oden, Gloria L. Vega, Lynn Gargan, and Daniel C. Bowers. Effect of Hypothalamic Radiation on Cardiometabolic Risk in Survivors of Childhood Brain Tumors. Poster presented at the 13th International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer. Memphis, TN. June 13-15, 2013.

Also presented at:
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Susan Y. Wu, Raven Cooksey, Amit Gode, Laura Klesse, Jon Oden, Gloria L. Vega, Lynn Gargan, Daniel C. Bowers. Cardiovascular Risk Factors and Bone Density Among Survivors of Pediatric Brain Tumors Exposed to Radiation. Poster presented at the Doris Duke Clinical Research Fellow Meeting. Herndon, VA. May 2013.

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CHAPTER ONE: INTRODUCTION

Brain tumors are the most common solid tumor of childhood, with approximately 2200 new cases each year [1]. With five-year survival rates currently exceeding 70% across all primary CNS tumor histologies [1], increasing attention has turned to evaluating the long-term sequelae of treatment, which may include a combination of surgery, chemotherapy, and radiation.

Late effects associated with cranial radiation exposure include decreased intellectual capacity as measured by intelligence quotient [2,3], differential growth in radiated compared to non-radiated tissues [4], increased risk of stroke [5], and hypothalamic-pituitary axis (HPA) hormone deficiencies [6]. Endocrine deficits accumulate in a dose- and volume-dependent fashion; irreversible growth hormone deficiency has been observed above 18 Gy [7,8] while gonadotropin, thyrotropin, and adrenocorticotropin deficiencies are seen at doses exceeding 40 Gy [9].

The majority of literature assessing late effects of radiation in childhood cancer survivors has been conducted in acute lymphoblastic leukemia (ALL) patients, and has identified components of metabolic syndrome, namely truncal obesity, increased blood pressure, insulin resistance, and dyslipidemia, in this population [10-14]. In adults, metabolic syndrome is associated with increased incidence of type-2 diabetes mellitus, and increased cardiovascular as well as all-cause mortality [15]. Two studies to date have demonstrated an increased prevalence of cardiometabolic risk factors, including dyslipidemia, hypertension, and obesity in pediatric brain tumor survivors [16,17], though these studies were relatively small and heterogeneous.

Leptin and adiponectin are fat-derived hormones that have been proposed to play a role in the development of metabolic syndrome. Leptin is a central signal of energy sufficiency; downstream effects include decreased caloric intake and increased energy output [18]. The hypothalamus is a primary site of leptin receptor gene expression—in particular the ventromedial

hypothalamus, dorsomedial hypothalamus, and arcuate nucleus [19]. In animal models, diet-induced leptin resistance selectively inhibits signaling cascades in neurons of the arcuate nucleus but not the ventromedial or dorsomedial hypothalamus, suggesting that the arcuate nucleus may be the primary site of central leptin resistance [20]. As leptin levels tend to correlate with fat mass, obese individuals often have elevated leptin levels, suggesting physiologic leptin resistance [21]. Adiponectin is inversely correlated with fat mass and is thought to improve insulin sensitivity through its interactions with the liver and skeletal muscle [22]. Taken together with leptin, the leptin:adiponectin ratio has emerged as a biomarker for assessing insulin resistance, cardiovascular risk, and systemic inflammation [23,24].

Pediatric brain tumor survivors are at risk for developing decreased bone mineralization, which is associated with gait abnormalities and increased fracture risk [25,26]. Data from the Childhood Cancer Survivor Study (CCSS) indicates that pediatric brain tumor survivors are 25 times more likely to report fractures compared to healthy siblings [6]. Similar to the literature on cardiometabolic risk, many studies examining bone density and body composition in childhood survivors of brain tumors have relied on relatively small and heterogeneous patient populations [26-28]. Mechanisms for the development of decreased bone density in these patients include endocrine deficits (particularly growth hormone deficiency but also gonadotropin deficiency, leading to decreased estrogen and testosterone levels), decreased weight bearing activity, concurrent chemotherapy, and use of glucocorticoids [29-32]. Hypothalamic radiation exposure may contribute to decreased bone density through damage to the HPA axis resulting in endocrine deficiencies as well as changes in energy expenditure [17,33].

Throughout the literature assessing late effects of radiation with regard to both cardiometabolic risk and bone density, endocrine deficiencies (particularly growth hormone deficiency) have been used as a proxy for hypothalamic damage. No studies to date have

examined the effect of radiation dose to the hypothalamic-pituitary axis (HPA) on cardiovascular risk or bone density [16].

The primary aim of this study was to investigate the role of HPA radiation in the development of cardiometabolic risk factors and metabolic syndrome as well as decreased bone density in pediatric brain tumor survivors. Implications for improved long-term follow-up care in this population include identifying more sensitive screening criteria and achieving a better understanding of treatment-related changes. Secondary aims included investigating the influence of additional variables on the development of cardiovascular risk factors and decreased bone density, namely age at diagnosis, age at the time of study, overall survival time, gender, radiation dose to the HPA, tumor histology, and tumor location. As leptin and adiponectin appear to mediate the development of insulin resistance and cardiovascular risk factors in adults [23], we also assessed the relationship between components of metabolic syndrome and leptin and adiponectin in this patient population.

CHAPTER TWO: EXPERIMENTAL PROCEDURES

Patient Selection:

Patients were identified through the Comprehensive Neuro-Oncology Long-Term Follow-Up Clinic at Children's Medical Center of Dallas; patients received information about the study by mail and were approached at the time of clinic visit to participate. All participants or their guardians signed informed consent to participate in the study.

Eligibility criteria included patients 1) under 18 years of age at the time of cancer diagnosis, 2) at least one year off treatment, which could include surgery, chemotherapy, or radiation, 3) 5–20 years old at the time of study, and 4) if radiated, they had to have received more than 20 Gy. Exclusion criteria included patients 1) with a prior diagnosis of type I diabetes mellitus, 2) diagnosis of neurofibromatosis or craniopharyngioma, 3) pregnant females, and 4) patients unable to fast. Patients were evaluated during their scheduled Comprehensive Neuro-Oncology Long-Term Follow-Up Clinic visit.

The Institutional Review Board of the University of Texas Southwestern Medical Center and The Simmons Cancer Center Protocol Review and Monitoring Committee approved and monitored this study.

Evaluations

Study assessments included vital signs (blood pressure, heart rate), anthropomorphic measurements (height, weight, and waist circumference at the level of the umbilicus and superior iliac crests in the standing position), fasting labs (lipid panel, insulin, C-peptide, glucose, leptin, adiponectin, and insulin-like growth factor-1 (IGF-1)), the Paffenbarger Physical Activity Survey [34], the MEDFICTS diet recall survey [35], and Dual-energy X-ray Absorptiometry (DXA) scan. Radiation treatment plans were reviewed by physicians in the Department of Radiation

Oncology at the University of Texas Southwestern Medical Center; patients who received 100 cGy or more of radiation to the hypothalamus were considered to have received measurable radiation to the HPA axis. Twenty-eight patients who received cranial radiation did not have treatment plans that could be reconstructed to verify HPA radiation exposure and were excluded from analyses looking at the effect of HPA radiation.

Insulin Resistance

Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR), as described by Matthew et al. [36], which utilizes a one-time fasting measurement of insulin and glucose to characterize insulin sensitivity and β-cell function. The formula for HOMA-IR is: $\frac{glucose\left(\frac{mg}{dL}\right) \times insulin\left(\frac{mU}{L}\right)}{405}$. HOMA-IR is of particular value in populations at risk for developing insulin resistance as it can identify individuals who have not yet developed fasting hyperglycemia, but are compensating with increased insulin production. Insulin resistance was defined as a HOMA-IR value ≥ 2.5 in prepubertal children (Tanner stage I) [37,38] and a HOMA-IR value ≥ 4.0 in pubertal patients (Tanner stage ≥ II) [39,40].

Metabolic Syndrome and Concomitant Cardiometabolic Risk

Metabolic syndrome was diagnosed based on the 2007 International Diabetes Federation (IDF) criteria for children and adolescents greater than 10 years of age (Table 1) [41]. Modified IDF criteria were utilized to identify concomitant cardiometabolic risk in children younger than ten years of age who met three of the five criteria (Table 1). This approach has been employed by numerous investigators and is particularly useful in younger patients as it evaluates criteria such as blood pressure and waist circumference using age, gender, and height-based percentiles [42-

45].

DXA Scan

Total body bone mineral content (TBBMC), total body bone mineral density (TBBMD), total body lean body mass (TBLBM), total fat mass, truncal fat mass, and fat free mass index (FFMI) were determined by whole body DXA scan using a Hologic Discovery W QDR Series scanner (Hologic Inc., Bedford, MA). Software used for analysis was APEX System version 2.3.1, which includes reference ranges for pediatric patients three years and older.

Bone mineral content (BMC) provides an assessment of the total grams of mineralized bone matrix, whereas bone mineral density (BMD) is BMC/area of the scanned bone [46]. Some literature suggests that BMD may be less accurate in children as it is influenced to a greater extent by bone size [47], but it is a measure commonly used in reference population values [48,49]. As such we have reported both measures.

The FFMI is a height-normalized assessment of obesity that takes into account body composition and is calculated as fat free mass/height^2 (kg/m^2). There is literature to suggest it captures a more nuanced view of body composition than BMI, which is unable to separate fat from non-fat compartments. For example, in children with growth hormone deficiency, six months of growth hormone repletion has been shown to increase fat free mass without corresponding changes in BMI [50]. The FFMI is also of particular interest in this patient population as there is literature to suggest that sedentary activity is associated with a low FFMI, while physical activity, in particular resistance training, is associated with increases in fat free mass [51,52].

TBBMD, TBBMC, and FFMI z-scores, normalized for age and gender, were calculated based on National Health and Nutrition Examination Survey (NHANES) data released in 2008

and available for children 8–20 years old; this limited z-score analysis to patients eight years and older. The calculator is publically available online through the Baylor College of Medicine Body Composition Laboratory and is based on correction factors derived by Kelly et al. [53]. For patients 20 years of age at the time of study (n = 4), z-score cut-off values for osteopenia and osteoporosis were -1.5 and -2.5 respectively. For patients under 20 years of age, z-score cut-off values were -1.0 and -2.0 for osteopenia and osteoporosis respectively [54].

Statistical Analysis

Two-tailed t-tests and chi-squared analysis were used to compare variables between patients who did or did not 1) receive HPA radiation, 2) meet criteria for metabolic syndrome or concomitant cardiometabolic risk, 3) meet criteria for osteopenia, and 4) have insulin resistance as measured by HOMA-IR. All statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). An α-value ≤ 0.05 was considered statistically significant.

CHAPTER THREE: RESULTS

Patient Summary

Of 171 eligible patients identified and invited to participate, 146 were consented and evaluated in this study (Table 2). The most common reasons for refusal to participate included: need for additional venipuncture (n = 8), patient or family preference (n = 8), concern regarding additional radiation exposure associated with the DXA scan (n = 2), or other (n = 7).

The average age at the time of study was 13.5 years (SD 3.9 years, range: 5-21 years) and mean survival time was 6 years (range: 1-16.6 years). One hundred thirty-nine patients underwent surgery, of which one patient was biopsied only. Eighty patients received chemotherapy. Seventy patients were treated with radiation, of whom forty-two had treatment plans that could be used to calculate dose to the hypothalamic-pituitary axis (HPA); 38 of these patients received >100 cGy to the HPA which was our cutoff for measurable radiation dose.

Metabolic Syndrome and Concomitant Cardiometabolic Risk

Metabolic syndrome was identified in seven survivors 10 years and older who met 3 of 5 criteria, four with HPA radiation exposure (4/26, 15%) and three without (3/46, 6.5%). Concomitant cardiometabolic risk, identified in patients 5–10 years of age who met 3 of 5 criteria, was found in four additional patients, three who received HPA radiation (3/12, 25%) and one who did not (1/30, 3.3%). Patients who received HPA radiation were more likely to meet criteria for metabolic syndrome or concomitant cardiometabolic risk than patients who did not receive HPA radiation (18.4% vs. 5.3%, p = 0.04) (Table 3).

Compared to patients who did not receive HPA radiation, those who did were more likely to have elevated triglycerides (24% vs. 8%, p = 0.02) and low HDL (32% vs. 14%, p = 0.04) (Table 3). There was no statistically significant difference between those with and without HPA

radiation with regard to elevated waist circumference (28% vs. 32%, p = 0.67), elevated systolic blood pressure (5% vs. 18%, p = 0.08), or elevated diastolic blood pressure (0% vs. 6%, p = 0.16). All patients but one had normal fasting glucose levels.

Patients who met criteria for metabolic syndrome or concomitant cardiometabolic risk were more likely to have impaired insulin sensitivity as measured by HOMA-IR (2.23 vs. 0.93, p < 0.001) and had decreased percent lean body mass (57% vs. 63%, p = 0.01) compared to patients who did not meet criteria (Table 5). Patients who met criteria also had higher BMI and BMI z-scores compared to those who did not (28.8 vs. 21.3, p < 0.001; 1.81 vs. 0.5, p < 0.001). These patients also had significantly greater truncal body fat percentage (38.8% vs. 30.2%, p = 0.005) but no significant difference in total body fat percentage (40.2% vs. 33.1%, p = 0.12).

Patients who met criteria for metabolic syndrome or concomitant cardiometabolic risk did not differ significantly in terms of gender distribution (63% vs. 51% male, $\chi^2 = 0.53$), age at diagnosis (7.8 vs. 6.5 years, p = 0.40), age at the time of study (13.7 vs. 12.0 years, p = 0.21), or overall survival time (5.8 vs. 5.3 years, p = 0.63) compared to those who did not meet criteria.

Insulin Resistance and Adipokines

Childhood brain tumor survivors exposed to HPA radiation did not have statistically significant differences in fasting blood glucose (mg/dL) or HOMA-IR compared to patients who did not receive HPA radiation (p = 0.88 and p = 0.23 respectively) (Table 4). However patients diagnosed with metabolic syndrome or concomitant cardiometabolic risk had elevated HOMA-IR values compared to those who did not meet criteria (2.23 vs. 0.93, p < 0.001). Patients with elevated HOMA-IR values also had significantly higher leptin levels (38.4 vs. 14.4 ng/mL, p = 0.001), lower adiponectin levels (6.8 vs. 15.1 μg/mL p = 0.04), and elevated leptin:adiponectin ratios (7.1 vs. 1.8, p = 0.001) (Table 9). Patients with elevated HOMA-IR values had greater

truncal body fat percentage (46% vs. 39%, p = 0.04) and lower percent lean body mass (56% vs. 64%, p = 0.03) despite no significant difference in percent body fat z-score (1.18 vs. 0.63, p = 0.19). There was no effect on diet as assessed using MEDFICTS score and insulin resistance. There was no difference in leptin or adiponectin levels, or leptin/adiponectin ratios in patients with and without HPA radiation exposure (p = 0.55, 0.98, 0.19 respectively) (Table 6).

Bone Mineral Content and Bone Mineral Density

HPA radiation exposure was associated with significantly lower TBBMC and TBBMD z-scores (-1.3 vs. -0.3, p = 0.003, and -1.4 vs. -0.2, p < 0.001 respectively) (Table 7). Patients who received HPA radiation were significantly more likely to meet criteria for osteopenia using TBBMC (56% vs. 23%, p = 0.004) and TBBMD z-scores (60% vs. 26%, p = 0.004). Similarly, patients who received HPA radiation were more likely to meet criteria for osteoporosis using TBBMC (37% vs. 8%, p = 0.002) and TBBMD z-scores (30% vs. 3.8%, p = 0.001). Patients who received HPA radiation also had lower FFMI z-scores (-1.4 vs. -0.1, p = 0.001).

Patients who met criteria for osteopenia using TBBMC z-score had greater maximum radiation dose to the HPA (3159 vs. 2629 cGy, p < 0.001) (Table 8). Patients who met criteria for osteopenia had lower BMIs (20.8 vs. 24.8, p = 0.001), lower BMI z-scores (0.005 vs. 1.06, p < 0.001), lower TBLBM (28.1 vs. 37.7 kg, p = 0.001), and lower FFMI z-scores (-1.62 vs. -0.06, p < 0.001) than those who did not have osteopenia. Patients who met criteria for osteopenia also had decreased physical activity as measured by the Paffenbarger physical activity score (2043 vs. 3278 kcal/week, p = 0.03). Patients who met criteria for osteopenia were not significantly different from those who did not met criteria with regard to gender (45% vs. 50% male, χ^2 = 0.82), age at diagnosis (8.4 vs. 7.7 years, p = 0.5), age at the time of study (13.6 vs. 13.7 years, p = 0.87), overall survival time (6.0 vs. 6.6 years, p = 0.56), truncal body fat percentage (31.6% vs.

32.6%, p = 0.66) or total body fat percentage (34.2% vs. 35.0%, p = 0.77).

Body Composition and Physical Activity and Diet

HPA radiation exposure was associated with decreased FFMI z-scores (-1.4 vs. -0.1, p = 0.001) (Table 7). Lower Paffenbarger physical activity scores were associated with decreased TBBMD z-scores ($p < 0.001$) and decreased percent lean body mass ($p=0.006$). In our patient population, body composition was not affected by MEDFICTS score.

CHAPTER FOUR: DISCUSSION

Childhood brain tumor survivors exposed to hypothalamic radiation are at increased risk of developing cardiometabolic risk factors that, while often subclinical, can be identified within the first decade after treatment. Significant attention has been directed at assessing the late effects of HPA radiation exposure due to the role of the hypothalamus in coordinating endocrine functions; the data presented here are consistent with the literature that suggests an increased prevalence of a metabolic syndrome-type phenotype in patients who received cranial radiation or who have hypothalamic damage as measured by endocrine deficiencies [16,17]. Our data are consistent with results from Pietila et al., which found that 4/20 patients (20%) who received radiation met criteria for metabolic syndrome; 18.4% (7/38) of patients with HPA radiation exposure in our study met similar criteria. We found the baseline prevalence of metabolic syndrome or concomitant cardiometabolic risk in patients who did not receive HPA radiation to be 5.3% (4/77), which is similar to the 4.5% prevalence identified by Ford et al. using NHANES 1999–2004 data and IDF criteria [55].

These results also illustrate characteristics of the metabolic syndrome phenotype, which has been well described in the literature [39,55], and support data which suggests that insulin resistance is directly correlated with serum leptin values and leptin:adiponectin ratio while and inversely correlated with adiponectin values in children and adults [23,56-59].

Though patients with metabolic syndrome or concomitant cardiometabolic risk were less likely to meet criteria for osteopenia, it is likely this effect was due to increased BMI in these patients, as increased body mass provides increased weight bearing activity, though adipocyte-mediated endocrine effects also play a role in bone homeostasis [60,61].

Increased visceral body fat, more so than increased subcutaneous fat, is associated with lower vitamin D levels [62]. Though visceral body fat cannot be directly measured by DXA,

there is literature that suggests that visceral fat may be correlated with truncal or abdominal fat as measured by DXA [63-65], in which case we would expect lower vitamin D levels, and potentially lower bone density, in patients with higher truncal body fat percentage—this was not the case in our patient population. Unfortunately, our evaluations did not include assessment of vitamin D level and thus we cannot further explore the effects of vitamin D on bone mineralization in this population.

As current follow-up guidelines for pediatric cancer survivors exposed to cranial radiation with regard to obesity-related complications and bone density include an annual physical exam with height, weight, BMI, and blood pressure measurements and post-fracture imaging respectively (with consideration for further testing) [66], our results suggest that additional assessments may be warranted for improved follow-up care. Height, weight, BMI and blood pressure measurements were similar between those who received HPA radiation compared to those who did not, while triglyceride and HDL levels and bone density were significantly different between the two groups, with potential long-term implications for cardiovascular health and fracture risk in this population.

Strengths and weaknesses

A key strength of this study is the large sample size. Even after excluding patients who did not have radiation treatment plans that could be assessed for HPA dose, we investigated 117 pediatric brain tumor survivors, more than twice that which has been previously reported with regard to cardiometabolic risk factors or bone density (n=52 [16,27], 26 [17], 36 [28], 27 (23 medulloblastoma and 4 other) [67], 16 [68], 61 craniopharyngiomas [69], 28 intracranial germ cell tumors [70], 16 medulloblastomas [71]). One study with a similar number of brain tumor survivors (n = 114) did assess vitamin D status and found no significant association with cranial

radiation exposure [72]. However this remains a very heterogeneous population and we remain limited in statistical power based on the number of patients recruited.

In this analysis, we used a composite outcome variable for patients who either met criteria for metabolic syndrome or were younger than 10 years of age who met three of five criteria to increase statistical power. Though similar criteria were met for both groups, these remain distinct endpoints. We felt that identifying dyslipidemia, insulin resistance, and altered body composition in the younger cohort had significant implications for follow-up care and that their inclusion was thus justified.

To our knowledge, this is the first study to specifically assess dose to the HPA in pediatric brain tumor survivors in the context of cardiometabolic risk factors and body composition. Literature assessing leptin and adiponectin and their roles in the development of obesity or metabolic syndrome is limited in children [24,58], and even more so among pediatric cancer survivors, with an emphasis on ALL survivors [57,73,74]. We were limited by the number of patients with leptin and adiponectin results; additional data would be helpful in assessing the potential role of leptin resistance in this population.

The inclusion of additional variables, in particular vitamin D and more detailed assessments of physical activity and dietary habits, would have been helpful in characterizing the associations described above. This study also assessed patients at a single time point; we do not know how cardiometabolic risk factors change over time and what their effects may be as patients enter adulthood.

Future direction

More work is needed to better characterize the mechanism by which pediatric brain tumor survivors develop cardiovascular risk factors and decreased bone density. Continued

monitoring is needed to assess the clinical manifestations of metabolic syndrome and decreased bone density as these patients age. As some data suggest that lifestyle changes can limit the development of metabolic syndrome [75], further study is required to develop interventions that can ameliorate the impact of such risk factors.

LIST OF TABLES

Table 1. Criteria for diagnosing metabolic syndrome or concomitant cardiometabolic risk

Criteria	**Age <10 years old**	**Age 10-15 years old***	**Age ≥ 16 years old***
Central obesity (waist circumference)	≥ 90 percentile for age and gender [45] (or ≥ adult cut-off, if lower)	≥ 90 percentile for age and gender (or ≥ adult cut-off, if lower) **	Females: ≥ 80 cm, Males: ≥ 90-94 cm (ethnic variation) **
Triglycerides	≥ 150 mg/dL	≥ 150 mg/dL	≥ 150 mg/dL
HDL	≤ 40 mg/dL	≤ 40 mg/dL	≤ 40 mg/dL
Blood Pressure	Systolic OR diastolic BP ≥ 90% age, gender, and height specific norm[76]	Systolic ≥ 130mmHg OR diastolic ≥ 85 mmHg	Systolic ≥ 130mmHg OR diastolic ≥ 85 mmHg
Fasting hyperglycemia	Fasting glucose ≥ 100 mg/dL OR known type 2 diabetes mellitus	Fasting glucose ≥ 100 mg/dL OR known type 2 diabetes mellitus	Fasting glucose ≥ 100 mg/dL OR known type 2 diabetes mellitus

***** International Diabetes Federation 2007 criteria for metabolic syndrome in pediatric patients [41]
****** Required for diagnosis

Table 2 – Description of 146 participating subjects

Subject Characteristic	**Value/Frequency (range, SD or %)**
Mean age at time of study	12.3 years (5-20 years, SD 4.1 years)
Mean age at diagnosis	6.3 years (0.1-18 years, SD 4.4 years)
Mean survival time	6 years (range 1-16.6 years)
Gender (male/female, % male)	82/64 (56% male)
Race/Ethnicity (%)	
Non-Hispanic white	80 (55%)
Hispanic	41 (28%)
Non-Hispanic Black	18 (12%)
Asian (includes South Asian)	5 (3%)
Other (includes biracial)	2 (1%)
Histology (%)	
Low-Grade Glioma (including pilocytic astrocytoma)	59 (40%)
High Grade Glioma (including oligodendroglioma, anaplastic astrocytoma)	4 (2.7%)
Brain stem glioma	3 (2.0%)
Ependymoma	10 (6.8%)
Choroid Plexus Tumor	4 (2.7%)
Ganglioglioma	4 (2.7%)
Medulloblastoma, PNET, ATRT	36 (24.6%)
Germ Cell Tumor	2 (1.4%)
Germinoma	8 (5.5%)
Other *	16 (11%)
Treatment modality (%)	
Surgery	139 (95%)
Chemotherapy	80 (55%)
Radiation therapy	70 (48%)
Received HPA radiation	38**
Mean dose to the HPA (cGy)	3036 cGy

Percentages may not add to 100 due to rounding
*includes pilomyxoid glioma, pineoblastoma, hemangiopericytoma, prolactinoma, DNET
**As not all treatment plans could be reconstructed to assess HPA dose, percentage not provided

Table 3. Chi-squared analysis in patients with and without HPA radiation exposure

Criteria	Patients with HPA radiation exposure (n=38)		Patients without HPA radiation exposure (n=76)		χ^2
	N	%	N	%	
Elevated waist circumference	11	27.5%	25	32%	0.67
Elevated triglycerides	9	24%	6	8%	**0.02**
Low HDL	12	32%	1	14%	**0.04**
Elevated fasting glucose	0	0%	1	1%	1.00
Elevated Systolic BP	2	5%	14	18%	0.08
Elevated diastolic BP	0	0%	5	6%	0.16
Elevated fasting glucose	0	0%	1	1.4%	1.0
Elevated HOMA-IR	2	5%	0	0%	0.11
Met criteria for metabolic syndrome or concomitant cardiometabolic risk	7	18.4%	4	5.3%	**0.04**

Table 4. Components of metabolic syndrome and BMI in patients with or without HPA radiation exposure

Criteria	Mean in patients exposed to HPA radiation (n=38)	Mean in patients not exposed to HPA radiation (n=76)	p-value
Waist circumference (cm)	80.4	79.1	0.75
BMI (kg/m^2)	21.7	22.2	0.70
BMI z-score	0.5	0.7	0.31
Systolic blood pressure (mmHg)	109.2	113.2	0.10
Diastolic blood pressure (mmHg)	63.3	64.6	0.40
Triglycerides (mg/dL)	105.1	86.3	0.08
HDL (mg/dL)	48.9	53.9	0.07
Fasting glucose (mg/dL)	80.0	78.0	0.88
HOMA-IR	1.2	0.9	0.23
C-peptide (ng/mL)	2.0	1.7	0.38

Table 5. Characteristics of patients who met criteria for metabolic syndrome or concomitant cardiometabolic risk compared to those who did not

	Met criteria (n=11)	**Did not meet criteria (n=103)**	**χ^2 or p - value**
Gender, % male	63%	51%	0.53
Mean age at diagnosis (years)	7.8	6.5	0.40
Mean age at time of study (years)	13.7	12.0	0.21
Mean survival time (years)	5.8	5.3	0.63
Treatment included surgery	81%	95%	0.14
Treatment included chemotherapy	55%	42.7%	0.53
Treatment included radiation	64%	31%	**0.04**
Maximum radiation dose to the HPA (cGy)	1935.8	1134.1	0.20
Fasting glucose (mg/dL)	77	79	0.52
HOMA-IR	2.23	0.93	**<0.001**
BMI	28.8	21.3	**<0.001**
BMI z-score	1.81	0.5	**<0.001**
Percent body fat, trunk	38.8	30.2	**0.005**
Percent body fat, total	40.2	33.1	0.12
Lean body mass (%)	57%	63%	**0.01**
Total body mass (kg)	71.6	49.4	**0.005**

Table 6. Adipokines in patients with or without HPA radiation exposure

Adipokine	Mean in patients exposed to HPA radiation (n=33)	Mean in patients not exposed to HPA radiation (n=66)	p-value
Leptin ((ng/mL)/kg body fat)	0.8	0.8	0.55
Adiponectin ((ug/mL)/kg body fat)	1.2	1.2	0.98
Leptin/adiponectin (ng/ug)	2.8	1.6	0.19

Table 7. DXA scan results in patients with or without HPA radiation exposure

DXA evaluation	Mean in patients exposed to HPA radiation (n=34)	Mean in patients not exposed to HPA radiation (n=63)	p-value
DXA % body fat, trunk	33.1	29.8	0.10
DXA % body fat, total	35.5	32.8	0.11
TBBMC z-score	-1.3	-0.3	**0.003**
TBBMD z-score	-1.4	-0.2	**< 0.001**
FFMI z-score	-1.4	-0.1	**0.001**
TBLBM (%)	61.6	64.0	0.16
IGF-1 z-score	-1.3	-0.3	**< 0.001**
Paffenbarger physical activity score (kcal/week)	2169.1	2577.6	0.36

Table 8. Findings in patients with and without osteopenia

	Patients with osteopenia (n=47)	**Patients without osteopenia (n=58)**	χ^2
Gender: % male	45%	50%	0.82
Treatment included surgery	90%	96%	0.62
Treatment included chemotherapy	41%	50%	0.46
Treatment included radiation	59%	24%	**0.005**
	Mean in patients with osteopenia	**Mean in patients without osteopenia**	**p-value**
Age at diagnosis (years)	8.4	7.7	0.5
Age at time of study (years)	13.6	13.7	0.87
Survival time (years)	6.0	6.6	0.56
Mean radiation dose to the HPA (cGy)	2629	812	**<0.001**
Maximum radiation dose to the HPA (cGy)	3159	2629	**< 0.001**
Leptin (ng/mL)	14.6	19.1	0.26
Adiponectin (μg/mL)	16.9	12.8	**0.05**
BMI (kg/m^2)	20.8	24.8	**0.001**
BMI z-score	0.005	1.06	**<0.001**
HOMA-IR	1.04	1.29	0.33
Truncal body fat (%)	31.6	32.6	0.66
Total body fat (%)	34.2	35.0	0.77
FFMI z-score	-1.62	-0.06	**<0.001**
Total fat mass (kg)	15.8	22.3	**0.01**
TBLBM (kg)	28.1	37.7	**0.001**
Lean body mass (%)	63	62	0.66
MEDFICTS diet recall score	59	60	0.86
Paffenbarger physical activity score (kcal/week)	2043	3278	**0.03**

Table 9. Elevated HOMA-IR associated with alterations in adipokines and body composition

	Elevated HOMA-IR (n=5)	**Normal HOMA-IR (n=133)**	**p-value**
Leptin (ng/mL)	38.4	14.4	**0.001**
Adiponectin (μg/mL)	6.8	15.1	**0.04**
Leptin:Adiponectin ratio	7.1	1.8	**0.001**
Percent body fat z-score	1.18	0.63	0.19
Truncal body fat (%)	46	39	**0.04**
Lean body mass (%)	56	64	**0.03**

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