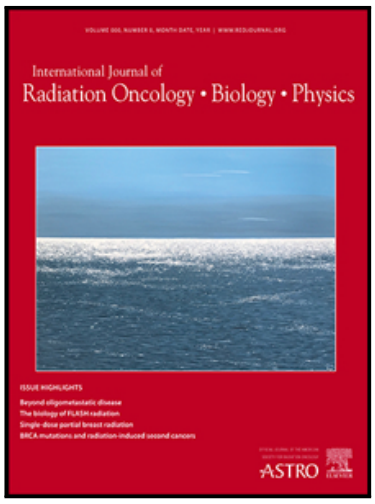

Effects of Proton Craniospinal Radiation on Vertebral Body Growth Retardation in Children

Myrsini Ioakeim-Ioannidou MD , Drosoula Giantsoudi PhD , Andrzej Niemierko PhD , Roshan Sethi MD , Daniel W Kim MD MBA , Torunn I Yock MD , Nancy J Tarbell MD , F. Joseph Simeone MD , Shannon M MacDonald MD

PII: S0360-3016(22)03212-6
DOI: https://doi.org/10.1016/j.ijrobp.2022.08.055
Reference: ROB 27815

To appear in: *International Journal of Radiation Oncology, Biology, Physics*

Received date: 10 November 2021
Revised date: 22 July 2022
Accepted date: 22 August 2022

Please cite this article as: Myrsini Ioakeim-Ioannidou MD , Drosoula Giantsoudi PhD , Andrzej Niemierko PhD , Roshan Sethi MD , Daniel W Kim MD MBA , Torunn I Yock MD , Nancy J Tarbell MD , F. Joseph Simeone MD , Shannon M MacDonald MD , Effects of Proton Craniospinal Radiation on Vertebral Body Growth Retardation in Children, *International Journal of Radiation Oncology, Biology, Physics* (2022), doi: https://doi.org/10.1016/j.ijrobp.2022.08.055

Running title: VB Growth Retardation following Proton CSI.

Effects of Proton Craniospinal Radiation on Vertebral Body Growth Retardation in Children.

Myrsini Ioakeim-Ioannidou MD[1], Drosoula Giantsoudi PhD[1], Andrzej Niemierko PhD[1], Roshan Sethi MD[1], Daniel W Kim MD MBA[1,] Torunn I Yock MD[1], Nancy J Tarbell MD[1], F. Joseph Simeone MD[2], Shannon M MacDonald MD[1]

Affiliations:

[1]Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

[2]Department of Diagnostic Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Author responsible for statistical analyses: Andrzej Niemierko, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114. Tel: (617) 724-9527; E-mail: aniemierko@mgh.harvard.edu

Corresponding author: Shannon M. MacDonald, MD, Massachusetts General Hospital, 55 Fruit St, Yawkey 112, Boston, MA 02114. Tel: (617) 643-7250; E-mail: smacdonald@partners.org

Conflicts of interest: TY has in kind support from MIM for a multicenter pediatric radiation oncology cancer registry. TY has NCI contracts, Institutional Grant Funding, and honorarium for two pediatric talks for IBA. The rest of the authors have no conflict of interest.

All data generated and analyzed during this study are included in this published article (and its supplementary information files).

Funding: This work was supported by Doris **Duke Fellowship.**

Abstract

Purpose: It is of great interest to physicians and patients/patients' families to be able to predict the amount of growth decrement following craniospinal irradiation (CSI). Little data exists on the impact of proton CSI. Our aim is to determine the effect of proton craniospinal irradiation (CSI) on vertebral body (VB) growth retardation, and to identify factors associated with growth delay.

Methods and Materials: We performed a retrospective outcome data analysis of 80 patients < 16 years old with central nervous system (CNS) tumors who received proton radiotherapy (PRT) at our institution between 2002 and 2010 with available spinal MRI imaging. Forty-eight patients received CSI, while 32 brain tumor patients that received focal cranial irradiation served as controls. Vertebral body height was measured midline using sagittal T1-weighted contrast or non-contrast enhanced MRI images of the spine. Measurements were repeated at multiple levels (C3, C3-C4, T4, T4-T5, C3-T6, T4-T7, L3, L1-L5) on available scans for the duration of follow-up. Data were fitted using a mixed-effects multivariable regression model, including follow-up time, CSI dose, age at CSI, and pre-treatment VB percentile as parameters.

Results: Median follow-up was 69.6 months for patients treated with proton CSI and 52.9 months for the control group. There was a significant association of CSI dose, follow-up time, age at treatment, and pre-treatment VB percentile with VB growth retardation. Growth retardation was shown to be independent of gender or growth hormone deficiency.

Conclusions: Although the current practice of PRT CSI delivery allows for sparing of the organs anterior to the spine, the vertebral column receives radiation therapy (RT) due to its close proximity to the targeted spinal canal. In growing children, the whole vertebral body has generally been included so that growth impairment is even across the VB. We present a

quantitative model predicting the growth retardation of patients treated with PRT CSI based on age at treatment, CSI dose, follow-up time, and pre-treatment growth percentile.

Manuscript

Introduction

Craniospinal irradiation (CSI) is a standard component of curative therapy for several childhood brain tumors including medulloblastoma, supratentorial primitive neuroectodermal tumors (PNET), germ cell tumors and other rare brain tumors. Long-term survivors are at risk of late complication from CSI.[1-3] A known side-effect of CSI is growth impairment of the vertebral column resulting in decreased sitting height for survivors.[1] Though protons offer an advantage over photons by sparing any tissue distal to the target volume allowing for decreased integral dose to non-target tissue such as the thyroid gland, esophagus, heart, lung, gastrointestinal tract, and ovaries, the vertebral column inevitability receives a higher radiation dose than most non-target tissues due to its close proximity to the spinal canal.[3-5]Traditional standard planning technique with protons for patients who have not reached their full growth potential includes the entire vertebral column in the treatment field in order to ensure that any arrest of growth is symmetric.[6-8]More recently, spinal canal irradiation with vertebral body sparing with proton therapy has been explored as a technique to allow for marrow sparing and more growth potential. Recent practice patterns show variation in vertebral body dosing for growing children among pediatric radiation oncologists.[9,10]

While it is known that CSI leads to growth impairment and decreased sitting height, little data exists about the degree of this growth decrement and the dose-response relationship and limited

data exists for PRT and growth impairment. Physicians are unable to predict for a given child the amount of growth impairment and it is not known if there exists a difference in growth impairment for protons versus photons. Only a handful of studies have examined growth findings following photon CSI as measured by individual or group vertebral bodies on baseline and follow up imaging studies.[11-13]

To our knowledge, we present the first study to compare pediatric patients treated with PRT CSI with a control non-CSI group and present a quantitative predictive model of growth retardation.

Methods and Materials

Patients and Treatment

The xxx Hospital institutional review board approved this retrospective review. Between February 2002 and October 2010, a total of 80 pediatric patients with CNS tumors and available baseline and follow up spinal MRIs were treated with passive scattering technique PRT at our institution. Our study included 48 patients who received PRT CSI treatment and 32 patients who received only cranial radiation and comprised our control group. Our inclusion criteria were 1) age at treatment <16 years old and 2) available spinal magnetic resonance imaging (MRI). We excluded patients who received surgical intervention or boost dose to the spine for metastatic disease. Specifically, we used MRI measurements as performed in Hartley et al[8] for a cohort of patients treated with proton CSI. We also used a control group consisting of patients who received focal brain radiation but underwent MRI of the spine in follow up (mainly ependymoma patients). This control group was chosen because of MRI availability and in order to see if there was still vertebral body impairment caused by other contributors such as growth hormone deficiency (GHD) and because a cohort of patients with sequential MRIs of the spine in healthy

children does not exist. We collected information about the patient's standing height, weight, pubertal status, and growth hormone status. These factors were incorporated into a multivariable analysis, in order to assess the impact of radiation dose.

Clinical data obtained via a retrospective review of medical records included demographics, primary malignancy, risk status for the medulloblastoma patients, pathology, chemotherapy, CSI dose, brain dose and volume for non-CSI patients, involved-field (IF) boost dose, posterior fossa (PF) dose, doses to the hypothalamus and the pituitary. We also recorded standing height, weight, and body mass index (BMI) before the delivery of RT along with the latest available standing height, weight and BMI following the completion of RT. Last but not least, we collected data GHD status and replacement therapy following the completion of RT.

Computed tomography (CT)-based 3-dimensional planning was used for each patient. All patients received proton therapy with passive scattering technique.

All CSI-patients (n=48) were treated in the prone position. The clinical target volume (CTV) for the whole brain followed conventional anatomical definition. The CTV for the spine included the thecal sac (defined as dura surrounding the spinal cord, cauda equine, and cerebrospinal fluid). Exiting nerves were included only until their emergence from the spinal foramina. Brain and spine fields were matched in a similar manner to the technique used for photon CSI, using a feathered junction that alternated every day across 3 locations. The whole VB was included to receive full dose. There was no A/P dose gradient across vertebral bodies at all levels. Posterior-anterior (PA) fields were used for the spinal portion of radiation and matched anterior to the spinal cord. Patients received an involved field (IF) boost, a whole posterior fossa (PF) boost or a sequential PF followed by IF boost. All non-CSI patients (n=32) were treated in the supine position with a partial brain field.

Vertebral Body Measurements

Serial MRI scans of the spine were obtained for each patient prior to treatment initiation and during follow-up (range, 5-154 months). MRIs were performed at our institution or were uploaded to the institutional picture archiving and communication system (PACS™; AGFA IMPAX, Morstel, Belgium). All measurements were performed on the PACS to ensure consistency and reproducibility. Vertebral body height was measured in the midline of the vertebral body in a craniocaudal direction perpendicular to the vertebral endplate using sagittal T_1-weighted contrast or non-contrast enhanced MRI images of the spine. For reproducibility, we measured the ossified portion of the vertebral body as the cartilaginous portion could not be readily differentiated from the intervertebral disk.

Measurements were obtained as follows:

Vertebral bodies C3, T4 and L3. Vertebral segments C3-C4, T4-T5, C6-T3, T4-T7, and L1-L5 measuring from the superior endplate of the highest level of the segment to the inferior endplate of the lowest endplate of the segment. Segments were measured aiming to limit the measurement error. All scans were measured by two investigators in consensus who were blinded to the patients' demographic and clinical characteristics. Measurements were all verified by a board-certified radiologist. In addition to measuring vertebral bodies, we collected the standing height pre-treatment and at each follow-up visit. These measurements were used for statistical analysis.

Statistical analysis

Clinical and treatment characteristics were summarized using descriptive statistics. Comparisons between baseline characteristics between CSI and non-CSI cohort were compared using

Pearson's chi-squared test for categorical variables, two sample t test for variables normally distributed, and Wilcoxon rank-sum test for variables with skewed distributions. A p-value ≤ 0.05 was considered statistically significant. Data analyses were performed using Stata 16 software (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC).

Modeling growth and growth retardation

The CSI-related VB growth retardation was estimated in relation to reference (normal) growth adjusted for baseline (pre-CSI) percentile. The reference growth curves for each of the eight VB segments as a function of age were estimated from combined all non-CSI VB measurements and baseline (pre-treament) CSI VB measurements. Published CDC reference statue-for-age growth curves are approximately linear up to the inflections point which is about 14 years of age for girls and 15 years for boys. [14,15] Since almost all our baseline and follow-up measurements were taken before the age of inflection on the growth curve, we modeled growth retardation during the linear part of the growth curve, that is up to 14 years for girls and up to 15 years for boys. According to the growth charts, the flattening of the growth curve for both boys and girls takes about 3 years. We decided to include more data points by using 14 years as a threshold for girls. In our exploratory analysis we tried a range of thresholds, and our decision was made based on our judgment of bias versus variance. To fit the reference growth data, we accounted for clustering structure of the data (or longitudinal character of the data) by using multilevel mixed-effects linear regression model with random effects at the patient level. To account for variation in the growth rate between patients our mixed-effects model included random slope for age at measurement variable. On multivariable mixed-effects model we did not find gender to be

statistically significantly associated with normal VB growth therefore age and GHD were the only independent variables of normal VB growth model.

We defined growth retardation as the difference between the measured VB length and the expected VB length for a given age and GHD status. Since different VB segments have different lengths and they grow over time we standardized growth retardation by expressing it as a percentage of the expected length (for a given age and GHD status). At any follow-up time the eight VB measurements represent growth status of a patient. Therefore, to maximize statistical power and to minimize VB measurement error we combined standardized growth retardation data for each patient at each follow-up time. That is, the average growth retardation over the eight VB segments was defined as the patient's growth retardation at any follow-up time. The patient's growth retardation data were fitted using a mixed-effects linear regression model with random effects at the patient level. To account for variation in the growth retardation rate between patients our mixed-effects model included random slope for follow-up time. To allow for non-linearity of growth retardation over time the follow-up time was modelled using fractional polynomials. Other investigated covariates included age at CSI, gender, GHD status, CSI dose, and a surrogate of baseline growth percentile expressed by pre-treatment growth retardation. Competing multivariable models of growth retardation were evaluated using Bayesian Information Criterion (BIC) and final parsimonious model included age at CSI, CSI dose, pre-treatment growth retardation, and fractional polynomial of follow-up time. We modelled vertebral body height for control group using mixed-effects model included random slope for age and with age, gender, and growth hormone deficiency as independent variables.

Results

Baseline measurements included 1,256 measurements collected from the non-CSI patients and 440 measurements collected from the CSI patients before the delivery of CSI. We collected 2,205 post-RT measurements for patients treated with CSI. In regular follow-ups after the completion of RT, we collected 2,205 measurements from the patients treated with CSI.

Patient clinical characteristics are summarized in Table 1. Our CSI-group consists of 20 female and 28 male patients, while the control group consists of 22 female and 10 male patients. Median age of patients at the time of diagnosis was 6 years (range: 2 – 12) and 5 years (range: 0.5 – 13) for the CSI and non-CSI cohorts, respectively. Thirty-nine of the patients who received proton CSI were treated for medulloblastoma, 5 for non-germinoma germ cell tumor (NGGCT), 2 for pure germinoma (PG), 1 for atypical teratoid/rhabdoid tumor (ATRT) and 1 for pinealoblastoma. Our control group consists of 25 patients treated for ependymoma, 6 patients with PG and 1 patient with NGGCT.

The median follow-up after completion of RT was 69.6 months (range: 12 - 156) for patients treated with proton CSI and 52.9 months (range: 24 – 120) for our control group.

Patient treatment characteristics are summarized in Table 2. The median CSI dose was 23.4 Gy (range: 18 – 36 Gy). In the CSI-group, 34 patients received involved field (IF) boosts, 10 patients received whole posterior fossa (WPF) boost, and 4 patients received both IF and WPF boost. All patients in the control cohort received IF boost. The median dose to the hypothalamus was 34.5 Gy (range: 22.6– 53.6) and 5 Gy (range: 0 – 50.8) for the CSI and non-CSI cohorts, respectively, and to the pituitary was 24.7 Gy (range: 18.5 – 52.7) for the CSI-group and 0.2 Gy (range: 0 – 45.7) for the non-CSI group.

Overall, the cohorts differ significantly in terms of gender distribution, type of malignancy, pre – RT BMI (the CSI-patients are slimmer), and doses to the hypothalamus and the pituitary (higher doses in CSI-group). Regarding the measured baseline VBs and VB segments, no statistically significant difference was found between study groups. No gap or junction overlap in cervical spine was found in our study population. Our imaging review showed no deformity that could affect our measurements.

In the CSI-group, 39 patients were found to have GHD at baseline, and 35 of those deficient patients received GH replacement therapy. In our control group, 8 patients were GH deficient and all of them began hormone replacement therapy. Using this data, we analyzed the effect of GH deficiency on growth and on growth impairment. We found that GH deficient patients on average had shorter VBs ($p = 0.02$ on two-sample Wilcoxon rank-sum test). This GHD effect persisted at any time post-CSI. However, the relative growth retardation resulting from CSI did not significantly differ between the patients who are GH deficient and those who are not.

Figure 1 shows VB growth data and mixed-effect linear regression fits for combined control cases and pre-RT CSI cases. Growth retardation for each VB and at each follow-up measurement was defined as the difference between the measured VB length and the reference VB length shown in supplemental figure. Growth retardation for each patient was defined as the average of growth deficiency values over the eight VB segments. The variation, as expressed by coefficient of variation (CV) was on average about 60% and is rather consistent across all patients. However, there is no systematic inter-VB variation that would indicate VB-specific sensitivity. Therefore, assuming that the existing variation is not systematic but random, we used the average over eight segments. That way we minimized the effect of random variation. A multivariable model of patient growth retardation included age at CSI, CSI dose, pre-CSI growth retardation,

and follow-up time (Supplemental material model). The non-linearity of growth retardation as a function of follow-up time is illustrated in Figure 2 for three ages at CSI and assuming CSI dose of 23.4Gy and no pre-CSI growth retardation. We would caution applying this model after a patient's growth spurt as we did not have enough measurements during and after that time to adequately model the nonlinearity and inter-patient variability of growth. The effect of CSI dose on expected growth retardation at age 15 is illustrated in figure 3A. Figure 3B illustrates the effect of age at CSI on expected growth retardation at age 15 assuming CSI dose of 23.4 Gy and no pre-CSI growth retardation. The dashed lines show 95% confidence intervals.

Discussion and Conclusion

This study represents the first report, to our knowledge, that quantitatively models vertebral body growth following PRT and its dependence on multiple parameters with a long-term follow up (median of 69.6 months). These findings may assist physicians and patient families to better understand what the likely growth effects will be based on CSI dose, age at treatment, GHD status and follow-up time. As more children are treated with proton CSI, this data also adds to the literature information on the late effects on growth from proton radiation.

Probert and Parker[6] reported on growth impairment following photon CSI as measured by sitting and standing height and found that children <6 years old were more sensitive to height impairment. In a study by Shalet et al[8], standing height, sitting height, and leg length were measured in 79 patients (aged 16-30 years), who had been given conventional CSI or cranial irradiation in childhood for a brain tumor and had completed their growth. Their measurements were compared with established standards for sitting height and leg length in British children (aged 16-18 years). They showed a linear relationship for age and loss in growth potential, estimating a 9 cm loss for radiotherapy delivered at 1 year of age to 5.5 cm loss for patients

receiving radiotherapy at 10 years of age.[8] The minimal dose to cause clinical growth impairment is not conclusive, but most series suggest a threshold of 15-25 Gy with a steep dose-effect relationship between 15-20 Gy and 35 Gy.[11,16] Hartley, et al.[11] reported on growth following photon radiotherapy CSI as measured by individual or grouped vertebral bodies on baseline and follow up imaging studies. The manuscript studied patients with medulloblastoma or supratentorial primitive neuroectodermal tumors under the age of 13 and found that growth was dependent on gender, age and dose of photon RT. A recent study by Oshiro et al[13] found that vertebral bone growth was significantly correlated with dose, and gradually decreased after >20 Gy, with a sharp decrease after 39 Gy. In contrast, age at time of treatment was not a significant factor for growth rate. Johnson et al[17] examined the impact of CSI on spine growth in pediatric medulloblastoma using either photon or electron, and they found that electron CSI had no significant difference in spine growth compared to the predicted spine growth based on previously published models with photon cohorts. [13] Mizumoto et al[12] recently published their results on the height impairment following photon CSI in pediatric patients with CNS embryonal tumors. CSI doses ≥36 Gy, female sex, younger age at CSI, and omitting hormone replacement were significantly associated with height impairment.[12] De et al[18] examined growth after PRT with or without the inclusion of the whole vertebral body by examining height z-scores before and after irradiation and found at a median follow up of 19 months that proton therapy including the entire vertebral body showed a greater reduction in height. In the aforementioned study[18], all patients (n=37) were treated with either whole VB proton CSI (n=21) or partial VB CSI (n=16), and growth changes were evaluated by comparing height at baseline and during follow-up visit. Target volumes along the entire spinal axis included whole VB in 67% and partial VB in 33%. Most common doses were 23.4, 36, and 18 Gy (RBE) used for 40%, 36%, and 16% of patients,

respectively. Boost RT to 1 or more sites was additionally given to all patients with cumulative median dose 54 Gy (RBE) [range, 18– 59.4 Gy (RBE)]. Baba et al[19] also investigated the relationship of the dose of proton beam therapy with subsequent growth of vertebral bodies in 23 children with a median age at treatment of 4 years old and a median observation period of 13.9 months. Outside of these studies, no other study has examined growth following proton CSI.

Similar to Hartley et al[11], we found that age and spinal dose significantly affected spinal growth and that some level of growth retardation was seen at all investigated dose levels. We intentionally used the same method of measurement as described by Hartley et to allow for some level of comparison to the most contemporary photon experience. Though a constant RBE value of 1.1 is used in proton therapy, comparison of the biological effect of CSI proton versus photon treatments to pediatric patients has not been well documented clinically or in large numbers of patients with long-term follow up. In contrast to Hartley et al[11], who studied 61 CSI patients and developed an overfitted model of 50 parameters, we compared 48 CSI patients to a control group of 32 non-CSI patients and we created a parsimonious predictive growth model with four parameters including follow-up time, CSI dose, age at CSI, and pre-CSI growth percentile.

The effect of gender on vertebral body growth has been previously described.[20,21] During both prepubertal and pubertal development, females tend to increase cortical thickness disproportionately to bone width in response to mechanical stress, whereas males do the opposite. Hormonal effects on growth plates also differ. Females begin their vertebral body growth spurt earlier (between ages 10-11) and peak by age 11. Males begin their vertebral body growth spurt later (near 12 years of age), and their peak is even further delayed, sometimes as late as 18 years of age.[21] Interestingly, some studies suggest that, in prepubertal children, before these hormonal effects are prominent, the difference between male and female vertebral body

volumes can be accounted for by height and weight alone[21]. However, in our analysis, similar to Baba et al[19], gender was not statistically significantly associated with growth nor with growth retardation caused by radiation. Therefore, our final growth retardation model does not include gender. Interestingly, we did find that the most substantial impact on growth delay was in the 5 years after RT, suggesting the possibility some recovery of growth after this period. This is hypothesis forming only and must be validated by additional studies. A study by Spiegler et al[22] reporting on the effect of cranial radiation on neurocognitive function over a prolonged survival period in pediatric brain malignancies showed early decline in intellectual functioning after treatment, and then an attenuation of that decline. Additional studies should explore and validate all of these findings that suggest some recovery.

Given the young age of patients and the possibility of cure, morbidity and toxicity of RT is of particular interest.[23,24] Studies have found short and long-term toxicity of RT, and in particular CSI, for pediatric brain tumors, including hematologic toxicities, cardiac disease, endocrine dysfunction, neurocognitive decline, ototoxicity, pulmonary disease, and secondary malignancies.[25-30] Unfortunately, the literature on detailed growth analyses following RT is limited. Similar to De et al[18], we found that age at treatment and RT dose are significantly associated with VB growth retardation. All patients in our study received whole VB proton CSI. Baba et al[19] found that bone growth retardation occurred even at a low dose of 10 Gy and that the growth rate linearly decreased as the dose increased without reaching a threshold value. In addition, no other factors had a significant impact on bone growth, including age and sex.[19]

Extracting growth retardation effect from follow-up measures of VB length is challenging because of complexity of the underlying radiobiological mechanisms of growth, significant inter-patient differences in normal growth, significant inter-patient differences in response to

radiation, and complex interplay of malignancy, GHD and GHD treatment on bone growth over time. Our multivariable fractional polynomial mixed-effects models represent a statistically sound approach to these challenging problems. Proton CSI allows for sparing of the organs anterior to the vertebral bodies, but standard technique still includes the entire vertebral body in the target for growing children. Although proton CSI allows avoidance of organs anterior to the vertebral bodies, it provides no advantage in marrow sparing or adverse effects of spine irradiation on growth or bone density for growing children. Advances in proton therapy including pencil beam scanning (PBS) and improvements in immobilization and set up verification now allow for delivery of proton CSI with substantial sparing of the vertebral bodies. Treatment planning techniques for vertebral body sparing (VBS) CSI have been recently published by XXX et al and demonstrate the feasibility of planning this treatment with substantial vertebral body sparing.[31] In addition, early clinical results for a small number of patients from Loma Linda indicate favorable outcomes and safety of a VBS technique that used less refined techniques.[9] De et al[18] also found that the inclusion of the whole vertebral body in younger proton CSI patients was associated with similar spinal curvature and more growth suppression as compared to partial vertebral body proton CSI. Further studies should explore the effects of VBS-CSI on growth retardation and spine curvature abnormalities and several institutions are investigating the use of VBS CSI on prospective trials (NCT03281889 and NCT04276194).

Limitations of our study include the small sample size, heterogenous patient population and therapeutic management, retrospective design, possible confounders such as GH replacement therapy, and the lack of data supporting the correlation between vertebral body height and standing height in adults. Extrapolation of this data for prediction of standing height is

unsupported.Therefore, we would caution applying this model for vertebral body measurements as our data cannot be interpreted into conclusions about standing height. Future studies should take these factors into account. As more studies with larger patient numbers look at quantitively understanding growth retardation, better predictive models can be built.

We quantitatively predict the growth retardation of pediatric patients treated with PRT CSI using follow-up time, age at treatment, CSI dose, and pre-treatment vertebral body for age percentile. We hope that this will assist in estimating growth impairment following proton CSI.

References

1. Probert JC, Lederman M, Bagshaw MA. Medulloblastoma--treatment and prognosis. A study of seventeen cases in ten years. *California medicine.* 1973;118(1):14-17.
2. Miralbell R, Lomax A, Russo M. Potential role of proton therapy in the treatment of pediatric medulloblastoma/primitive neuro-ectodermal tumors: spinal theca irradiation. *Int J Radiat Oncol Biol Phys.* 1997;38(4):805-811.
3. Walter AW, Mulhern RK, Gajjar A, et al. Survival and neurodevelopmental outcome of young children with medulloblastoma at St Jude Children's Research Hospital. *J Clin Oncol.* 1999;17(12):3720-3728.
4. Miralbell R, Lomax A, Bortfeld T, Rouzaud M, Carrie C. Potential role of proton therapy in the treatment of pediatric medulloblastoma/primitive neuroectodermal tumors: reduction of the supratentorial target volume. *International journal of radiation oncology, biology, physics.* 1997;38(3):477-484.
5. St Clair WH, Adams JA, Bues M, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys.* 2004;58(3):727-734.
6. Probert JC, Parker BR. The effects of radiation therapy on bone growth. *Radiology.* 1975;114(1):155-162.
7. Probert JC, Parker BR, Kaplan HS. Growth retardation in children after megavoltage irradiation of the spine. *Cancer.* 1973;32(3):634-639.
8. Shalet SM, Gibson B, Swindell R, Pearson D. Effect of spinal irradiation on growth. *Archives of disease in childhood.* 1987;62(5):461-464.
9. MacEwan I, Chou B, Moretz J, Loredo L, Bush D, Slater JD. Effects of vertebral-body-sparing proton craniospinal irradiation on the spine of young pediatric patients with medulloblastoma. *Adv Radiat Oncol.* 2017;2(2):220-227.
10. Medek S, De B, Pater L, et al. Practice Patterns Among Radiation Oncologists Treating Pediatric Patients With Proton Craniospinal Irradiation. *Pract Radiat Oncol.* 2019;9(6):441-447.

11. Hartley KA, Li C, Laningham FH, Krasin MJ, Xiong X, Merchant TE. Vertebral body growth after craniospinal irradiation. *Int J Radiat Oncol Biol Phys.* 2008;70(5):1343-1349.
12. Mizumoto M, Oshiro Y, Pan H, et al. Height after photon craniospinal irradiation in pediatric patients treated for central nervous system embryonal tumors. *Pediatr Blood Cancer.* 2020;67(10):e28617.
13. Oshiro Y, Mizumoto M, Pan H, Kaste SC, Gajjar A, Merchant TE. Spinal changes after craniospinal irradiation in pediatric patients. *Pediatr Blood Cancer.* 2020;67(12):e28728.
14. NIH Growth Chart

Accessed.
15. NIH Growth Chart.
16. Paulino AC, Wen BC, Brown CK, et al. Late effects in children treated with radiation therapy for Wilms' tumor. *International journal of radiation oncology, biology, physics.* 2000;46(5):1239-1246.
17. Johnson SB, Hung J, Kapadia N, Oh KS, Kim M, Hamstra DA. Spinal Growth Patterns After Craniospinal Irradiation in Children With Medulloblastoma. *Pract Radiat Oncol.* 2019;9(1):e22-e28.
18. De B, Cahlon O, Sine K, Mah D, Hug EB, Wolden SL. Early Axial Growth Outcomes of Pediatric Patients Receiving Proton Craniospinal Irradiation. *J Pediatr Hematol Oncol.* 2018;40(8):574-579.
19. Baba K, Mizumoto M, Oshiro Y, et al. An Analysis of Vertebral Body Growth after Proton Beam Therapy for Pediatric Cancer. *Cancers (Basel).* 2021;13(2):349.
20. Barlow T, Carlino W, Blades HZ, et al. The role of bone shape in determining gender differences in vertebral bone mass. *J Clin Densitom.* 2011;14(4):440-446.
21. Schober HC, Kreutzer HJ, Terpe R, et al. Radiograph-based study of gender-specific vertebral area gain in healthy children and adolescents as a function of age, height, and weight. *J Clin Densitom.* 2012;15(4):443-453.
22. Spiegler BJ, Bouffet E, Greenberg ML, Rutka JT, Mabbott DJ. Change in neurocognitive functioning after treatment with cranial radiation in childhood. *J Clin Oncol.* 2004;22(4):706-713.
23. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin.* 2014;64(2):83-103.
24. Zeltzer PM, Boyett JM, Finlay JL, et al. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. *J Clin Oncol.* 1999;17(3):832-845.
25. Liu KX, Ioakeim-Ioannidou M, Susko MS, et al. A Multi-institutional Comparative Analysis of Proton and Photon Therapy-Induced Hematologic Toxicity in Patients With Medulloblastoma. *Int J Radiat Oncol Biol Phys.* 2021;109(3):726-735.
26. Eaton BR, Esiashvili N, Kim S, et al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. *Neuro Oncol.* 2016;18(6):881-887.
27. Saha A, Salley CG, Saigal P, et al. Late effects in survivors of childhood CNS tumors treated on Head Start I and II protocols. *Pediatr Blood Cancer.* 2014;61(9):1644-1652; quiz 1653-1672.
28. Jakacki RI, Goldwein JW, Larsen RL, Barber G, Silber JH. Cardiac dysfunction following spinal irradiation during childhood. *J Clin Oncol.* 1993;11(6):1033-1038.
29. Huang TT, Chen Y, Dietz AC, et al. Pulmonary outcomes in survivors of childhood central nervous system malignancies: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer.* 2014;61(2):319-325.

30. Yock TI, Yeap BY, Ebb DH, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. *Lancet Oncol.* 2016;17(3):287-298.
31. Giantsoudi D, Adams J, MacDonald SM, Paganetti H. Proton Treatment Techniques for Posterior Fossa Tumors: Consequences for Linear Energy Transfer and Dose-Volume Parameters for the Brainstem and Organs at Risk. *Int J Radiat Oncol Biol Phys.* 2017;97(2):401-410.

Figure 1. VB growth data and mixed-effect linear regression fits for combined control cases and pre-RT CSI cases. Growth retardation for each VB and at each follow-up measurement was defined as the difference between the measured VB length and the reference VB length. The blue dots represent 87 mean values (mean value was calculated over 8 segments for each patient) for 30 patients.

Figure 2. Growth retardation as a function of follow-up time. Note the greater impact of growth retardation in the first 5 years following RT. We would caution applying this model after a patient's growth spurt.

Figure 3. A) The effect of CSI dose on expected growth retardation at age 15. B) The effect of age at CSI on expected growth retardation at age 15. The dashed lines represent 95% confidence intervals.

Table 1. Patient Characteristics

	48 CSI patients	32 Non-	P-
Age at Diagnosis (y)			0.14
Median (min-max)	6 (2 – 12)	5 (0.5 –	
Range **(IQR)**	4.5 – 8	2 – 9	
Age at RT (y)			0.16
Median (min-max)	6.6 (2 – 12)	5.8 (1 –	
Range **(IQR)**	5.0 – 8.9	2.5 –	
Age at last fu measurement (y)			
Median (min-max)	12.4 (6 – 14)	10.9 (4	0.038
Range **(IQR)**	9.8 – 13.3	7.2 – 12.9	
Sex			0.017
Male	28 (58%)	10	
Female	20 (42%)	22	
Malignancy			<0.001
Medulloblastoma	39 (81%)	0 (0%)	
Germ cell tumors (PG, NGGCT)	7 (15%)	7 (22%)	
ATRT	1 (2%)	0 (0%)	
Pinealoblastoma	1 (2%)	0 (0%)	
Ependymoma	0 (0%)	25 (78	
Time from RT to last FU (m)			0.054
Median (min-max)	69.6 (12- 156)	52.9 (24	
Range **(IQR)**	42.4 – 89.5	37.1 –	
No. of MRI scans			0.26
Median	5	4	
Range **(IQR)**	4 - 6	3 – 6.5	

Table 2. Radiation Treatment Doses

	48 CSI patients	32 Non-	P-value
CSI dose (Gy)			
0	0 (0%)	32 (100%)	
18	5 (10%)	0 (0%)	
21	1 (2%)	0 (0%)	
21.6	2 (4%)	0 (0%)	
23.4	32 (67%)	0 (0%)	
27	2 (4%)	0 (0%)	
36	5 (10%)	0 (0%)	
Boost (Gy)			
Involved-field (IF) only	34 (71%)	32 (100%)	
Posterior Fossa (PF) only	10 (21%)	0 (0%)	
Both IF and PF	4 (8%)	0 (0%)	
Mean Hypothalamus Dose (Gy)			<0.001
Median (min-max)	34.5 (22.6 – 53.6)	5 (0 –	
Range **(IQR)**	24.9 – 42.8	0 – 36.2	
Max Hypothalamus Dose (Gy)			<0.001
Median (min-max)	45.7 (24 – 55.4)	21.8 (0 –	
Range **(IQR)**	30.0 – 52.8	0.1 – 46.6	
Mean Pituitary Dose (Gy)			<0.001
Median (min-max)	24.7 (18.5 – 52.7)	0.2 (0 –	
Range **(IQR)**	24.1 – 36.5	0 – 25.4	
Max Pituitary Dose (Gy)			<0.001
Median (min-max)	27.8 (22.5 – 55)	2.1 (0 –	
Range **(IQR)**	27.4 – 40.7	0.1 – 38.1