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VERTEBRAL BODY GROWTH AFTER CRANIOSPINAL IRRADIATION

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Purpose: To estimate the effects of radiotherapy and clinical factors on vertebral growth in patients with medulloblastoma and supratentorial primitive neuroectodermal tumors treated with craniospinal irradiation (CSI) and chemotherapy.
Methods and Materials: The height of eight individual or grouped vertebral bodies (C3, C3-C4, T4, T4-T5, C6–T3, T4–T7, L3, L1–L5) was measured before and after CSI (23.4 or 36–39.6 Gy) in 61 patients. Of the 61 patients, 40 were boys and 21 were girls (median age, 7 years; range, 3–13 years), treated between October 1996 and October 2003. Sagittal T_1-weighted magnetic resonance images were used for the craniocaudal measurements. The measurements numbered 275 (median, 5/patient; range, 3–7). The median follow-up after CSI was 44.1 months (range, 13.8–74.9 months).
Results: Significant growth was observed in all measured vertebrae. Excluding C3-C4, the growth rate of the grouped vertebrae was affected by age, gender, and CSI dose (risk classification). The risk classification alone affected the growth rates of C3 ($p = 0.002$) and L3 ($p = 0.02$). Before CSI, the length of all vertebral bodies was an increasing function of age ($p < 0.0001$). The C3 length before CSI was affected by gender and risk classification: C3 was longer for female ($p = 0.07$) and high-risk ($p = 0.07$) patients.
Conclusion: All vertebrae grew significantly after CSI, with the vertebrae of the boys and younger patients growing at a rate greater than that of their counterparts. The effect of age was similar across all vertebrae, and gender had the greatest effect on the growth of the lower cervical and upper thoracic vertebrae. The effect of the risk classification was greatest in the lumbar spine by a factor of ≤10. © 2008 Elsevier Inc.

Radiotherapy, Radiation tolerance, Medulloblastoma, Primitive neuroectodermal tumor, Growth, Pediatrics.

INTRODUCTION

Postoperative craniospinal irradiation (CSI) is used in combination with chemotherapy to treat the most common malignant pediatric brain tumors, including medulloblastoma and supratentorial primitive neuroectodermal tumor (PNET). Overall survival rates of >70% have been achieved when measured at 5 years. However, the quality of survival for these patients is diminished by the treatment-related side effects. Spinal deformity and short stature have long been observed in children who have undergone CSI. Most have linear growth abnormalities (1). In 1975, Probert and Parker (2) published their work of children receiving >35 Gy and <25 Gy to the spine. They followed 29 children and recorded their sitting and standing heights as a function of time. They concluded that children <6 years old who had undergone radiotherapy (RT) to the spine are more sensitive to the deleterious height impairment effects of radiation and that this effect is seen with total doses as low as 25 Gy. Shalet *et al*. (3) observed similar impairments in growth. Although this late effect of radiotherapy is well known, no model of the expected linear growth after CSI is available. Furthermore, earlier studies have used the sitting and standing height as a composite measure to assess patients' growth. The radiation effects on individual vertebral body growth have not been evaluated. We hypothesized that the radiation dose would be inversely related to bone growth and that the expected growth after CSI would correlate with patient age at RT, the risk classification, and gender. Modeling the radiation-related treatment effects such as bone growth in children subjected to CSI is important because it might improve the selection of patients for risk-adapted strategies that seek to reduce the side effects of treatment.

METHODS AND MATERIALS

Patients and treatment

The institutional review board at St. Jude Children's Research Hospital approved this retrospective review. A total of 61 patients with medulloblastoma or supratentorial PNET treated between

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1996 and 2003 were included who met the following criteria: age at CSI of ≤13 years, minimal follow-up of 3 years with spinal magnetic resonance imaging (MRI), and no surgical or metastatic spinal intervention or destruction. All patients received a similar chemotherapy regimen that included dose-intensive cyclophosphamide, cisplatin, and vincristine. The patients were classified as being at high risk if neuraxis metastatic disease or residual tumor at the primary site >1.5 cm^2 was present or at average risk in the absence of these features. The average-risk patients received 23.4 Gy to the neuraxis, and high-risk patients received 36–39.6 Gy. Of the 26 high-risk patients, 5 received supplemental ''boost'' spinal RT for M3 disease. In 2 patients, the boost encompassed T9–T12, which was not a measured segment. In 2 patients, the boost included 10.8 Gy to the lumbosacral spine (1 boy and 1 girl). In 1 female patient, T4 received a supplemental dose of 5.4 Gy.

Our cohort included 40 boys and 21 girls. The median age at the start of RT was 7 years (range, 3–13 years). Of the 61 patients, 35 (57%) were average risk and 26 (43%) high risk. The high-risk patients were younger at the start of RT than the average-risk patients (6.8 years vs. 8.4 years, $p = 0.037$). The total number of spinal MRI evaluations reviewed for this study was 275 (median, 5/patient; range, 3–7). The median follow-up after radiotherapy was 44.1 months (range, 13.8–74.9 months).

Vertebral body measurement

Spinal MRI examinations were available for each patient before RT and were repeated every 12 months (range, 8–13 months) for ≤5 years after therapy. Contrast-enhanced or non–contrast-enhanced T_1-weighted sagittal images acquired at 1.5 T were used for all measurements. These scans were performed using a 3-mm slice thickness with no skip. The patients' data were queried by medical record number from the institutional picture archiving and communication system, and the scans were measured by a reviewer who was unaware of patient age, gender, and risk classification. The serial images were viewed side by side, and the heights of the vertebral bodies and vertebral segments were measured at midline in a craniocaudal direction with a straight line parallel to the posterior margin of the vertebral bodies. In addition to the measurements of the individual vertebral bodies, measurements spanning several vertebral bodies were obtained in an effort to control for measurement error. Measurements to the nearest 0.01 cm were obtained using a picture archiving and communication system viewer at the C3, C3–C4, T4, T4–T5, C6–T3, T4–T7, L3, and L1–L5 levels. These measurements and the corresponding date of the examination were recorded and submitted for statistical analysis.

Statistical analysis

The main goal of the statistical analysis was to investigate the effect of the radiation dose and clinical factors on the growth of selected vertebral bodies in prepubertal patients with medulloblastoma and supratentorial PNET. We developed a growth model for these patients to estimate the effect of age at RT, gender, and risk classification on the growth of the individual and grouped vertebral bodies. We used a mixed model with a random intercept (baseline, which differed among patients) and slope to estimate the growth of the vertebral bodies. In the models with multiple covariate variables, the slope (growth rate) was considered as a fixed effect, because the slopes were very similar among patients who had same values of covariate variables, and an estimate of the variation in slope was essentially zero in the fitted models with a random slope (4). We fit both models with fixed and random slopes, and the two models produced very similar results. We have reported the results from the model with fixed slope for simplicity. To analyze the effects of age at RT, gender, and risk classification (average vs. high risk) on the intercept and slope of the growth curves for different vertebrae, we fit linear mixed models with these as covariate variables, only the significant and the ''partially'' significant ones ($p < 0.10$) of those were retained in the final estimating equations. All analyses were performed using Statistical Analysis Systems software (SAS Institute, Cary, NC) (4). The p values were not adjusted for multiple testing.

RESULTS

Growth profiles of vertebral bodies after CSI

We first estimated the mean growth profiles of eight individual or grouped vertebrae without any covariate other than time. The mean baseline length and growth rate of the growth profiles are listed in Table 1. The general form of the model for growth profiles was as follows: vertebral body or segment length = baseline length + growth rate × time, where time denotes the follow-up in months after the start of RT, baseline length is the average length of the vertebral body at the start of RT, and growth rate is interpreted as the average length that a particular region of interest would grow during a 1-month period. All measured segments or individual bodies grew with time ($p < 0.0001$).

Growth models with age, gender, and risk classification as covariates

We created a model in which the baseline length and growth rate of the growth profiles for the individual and

Table 1. Growth after craniospinal irradiation for selected vertebrae

Vertebral body or segments	Baseline length (cm)			Growth rate (cm/mo)		
	Estimate	SE	p	Estimate	SE	p
C3	0.588	0.0172	<0.0001	0.002	0.0004	<0.0001
C3–C4	1.744	0.0383	<0.0001	0.004	0.0004	<0.0001
T4	1.041	0.0256	<0.0001	0.002	0.0003	<0.0001
T4–T5	2.594	0.0540	<0.0001	0.004	0.0005	<0.0001
C6–T3	6.172	0.1214	<0.0001	0.010	0.0010	<0.0001
T4–T7	5.796	0.1266	<0.0001	0.009	0.0009	<0.0001
L3	1.640	0.0334	<0.0001	0.004	0.0005	<0.0001
L1–L5	11.525	0.2384	<0.0001	0.021	0.0017	<0.0001

Abbreviation: SE = standard error.