Scientific Article

Comparison of height and weight after 12 vs. 18 Gy cranial radiation therapy in pediatric acute lymphoblastic leukemia (ALL) patients

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Abstract

Purpose: To compare the effect of 12 versus 18 Gy cranial radiation therapy (RT) on height and weight indices among pediatric patients with acute lymphoblastic leukemia (ALL).

Methods and materials: Records of children with ALL who were 2 to 14 years old at the time of RT and were treated at a single institution between 2000 and 2011 were reviewed. Patients' height, weight, and body mass index were converted into z-scores using the Centers for Disease Control growth charts to normalize the values to number of standard deviations from the mean. These values were measured at the pre-RT clinic visit and subsequent yearly intervals. The z-scores of the growth indices were fitted into a generalizing estimating equations model and analyzed by various clinical factors.

Results: A total of 48 patients met the study criteria, including 32 boys and 16 girls. The median age at the time of RT was 7 years (range, 2-14 years). Patients were separated into 2 dose groups: 12 Gy (n = 30) and 18 Gy (n = 18). Median follow-up was 4.9 years (range, 3.0-11.8 years) and 6.0 years (range, 3.1-10.5 years) and the median pre-RT height z-scores were −0.55 (range, −2.2 to 1.4) and −0.85 (range, −3.1 to 0.8) for the 2 groups, respectively (P = .65). Patients who received 18 Gy had a significant difference in change in height compared with those who received 12 Gy, who were able to maintain normal growth during the first 3 years of follow-up. This did not appear to be sex-specific, and there was no difference in change in weight or body mass index.

Conclusions: Compared with 18 Gy, patients with ALL who received 12 Gy of cranial RT had less height impairment in the first 3 years post-RT, but further prospective studies are needed.
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Introduction

Prior to the implementation of systematic central nervous system (CNS) prophylaxis, the CNS accounted for 50% to 70% of all relapses in patients with acute lymphoblastic leukemia (ALL).[1,2] Radiation therapy (RT), initially using craniospinal irradiation, is effective in preventing CNS relapses when given after chemotherapy-induced remission and can be used as salvage therapy for post-chemotherapy CNS relapses.[3] However, as the cure rates for pediatric patients with ALL have steadily improved due to better chemotherapy regimens, the long-term complications of RT are now increasingly relevant. Studies have investigated radiation dose de-escalation or even the complete omission of RT to limit normal tissue toxicities without compromising tumor control.[4,5]

One of the major toxicities of pediatric ALL treatment is height and weight abnormalities, which is attributed to the combination of chemotherapy drugs, corticosteroids, and RT needed to treat the disease. Radiation is known to have a dose-volume effect based on the amount of dose delivered and the volume of tissue radiated. Because craniospinal irradiation requires treating almost the entire vertebral column, substituting a combination of intrathecal chemotherapy and cranial RT can prevent the height loss caused by spinal RT but not the RT dose to the hypothalamus and pituitary gland.[6]

Given these concerns, prophylactic cranial RT doses were reduced from 24 Gy to 18 Gy in the hope of mitigating cognitive and growth dysfunction.[7−10] However, studies have shown that even 18 Gy still has a detrimental effect on height.[11−16] Current treatment protocols have now decreased the prophylactic dose to 12 Gy while still maintaining good control of the CNS.[17,18] Few studies have looked at the effect of 12 Gy cranial RT on growth. Two published studies concluded that ≥12 Gy cranial RT is associated with height impairment when compared with chemotherapy alone. However, given the small number of children who received 12 Gy in these studies, it remains unclear if there is a difference in height when compared with those who were treated with 18 Gy.[19,20]

Limited data are available regarding the effect of 12 to 18 Gy on weight. Obesity is a known complication after RT for brain tumors, where the prescribed dose typically varies from 40 Gy to 60 Gy.[21,22] We present a study cohort of pediatric patients with ALL who were treated with 12 Gy cranial RT with at least 3 years of follow-up and compare them with patients who received 18 Gy cranial RT.

Methods and materials

This study protocol was reviewed and approved by our institutional review board. Forty-eight patients who were treated between 2000 and 2011 met the following study criteria: aged 2 to 14 years with a diagnosis of either ALL or T-cell lymphoblastic lymphoma (treated according to an ALL protocol); received 12 Gy, 12.6 Gy, or 18 Gy of cranial RT; had a >2 cm increase in height over the past year prior to diagnosis; had no history of spinal RT; and had premenarchal status for female patients. Patients who received total body irradiation after cranial RT were eligible if the total body irradiation was administered more than 3 years after cranial RT. Patients were treated with chemotherapy regimens on or according to cooperative group protocols.

Medical records were reviewed to obtain clinical parameters and patients' height, weight, and body mass index (BMI) as measured at the preradiation clinic visit and subsequent yearly intervals in the survivors' clinic. These growth measurements were converted into a z-score using the Centers for Disease Control's growth charts (for 2 to 20 years old) to normalize the measurements to the number of standard deviations from the population mean according to height and sex. Descriptive statistics were performed using median, range, or frequency as appropriate. The 2 RT-dose groups were compared using the χ^2 test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. For the purpose of this study, patients who received 12.6 Gy in 7 fractions were classified in the 12 Gy group.

Changes in the growth indices (z-scores) were calculated from the initial visit (ie, pre-RT) at each visit over 3 years. The generalized estimating equation (GEE) model is used when inferences about the population-average are the focus for longitudinal data. In this study, the average difference in z-scores between 12 Gy and 18 Gy was our interest, not the difference for any individual patient or random effects. To assess the association between RT dose and clinical characteristics on the changes in the growth z-scores, the GEE model was used with normal distribution. An exchangeable correlation structure was assumed for the final GEE model and incorporated visit time, RT dose, sex, and age at the time of RT.

Patients' charts were also reviewed for evidence of further growth hormone (GH) deficiency workup, including blood testing for insulin-like growth factor-1 and insulin-like growth factor binding protein-3, clinical referral to the endocrinology clinic, or initiation of GH supplementation. All statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC). A P-value $< .05$ was considered statistically significant.

Results

Patient characteristics

A total of 48 patients (32 boys and 16 girls) met the study criteria. The median age at diagnosis was 6 years (range, 1-14 years) and the median age at start of RT was 7 years (range, 2-14 years). Girls had a median age at the start of RT of 6 years (range, 2-12 years) versus 9 years for boys (range, 2-14 years). Patients were separated into 2 dose groups: 12 Gy (n = 30) and 18 Gy (n = 18). The patient characteristics for these groups are shown in Table 1. The median follow-up was 4.9 years (range, 3.0-11.8 years) for the 12 Gy group and 6.0 years (range, 3.1-10.5 years) for the 18 Gy group. The median pre-RT height z-scores were -0.55 (range, -2.2 to 1.4) and -0.85 (range, -3.1 to 0.8) for the 2 groups, respectively ($P = .65$). The majority of the patients in the 12 Gy dose group received cranial RT with a 1.5 Gy fraction size compared with the 18 Gy group, which had more patients who were treated with 2.0 Gy fraction size ($P < .0001$). Sex and ethnicity were well balanced between the 2 groups.

Univariate analysis and multivariable GEE model

Univariate analysis showed that of the many clinical parameters studied, only the dose of radiation was statistically significant for the change in height indices (Table 2). From this analysis, the data was fitted to a GEE model correcting for visit time, dose, sex, and age at the time of RT. In the multivariable GEE model (Table 3), both dose and age at the time of RT were considered statistically significant. The 12 Gy dose was associated with a 0.252 average increase in z-score when compared with the 18 Gy dose. When plotting the change in height z-scores over time (Fig 1), the clinical benefit of 12 Gy remains present over all 3 years with the change in height z-scores at ≥ 0, but patients who received 18 Gy had a negative change in height z-scores. During the same time period, no significant change was seen in either weight index or BMI.

Sex and age analysis

Given that previous studies have shown an increased sensitivity of girls to cancer therapy, we analyzed the differential effect of the radiation dose in girls and boys. The clinical advantage of 12 Gy was similar in both girls

Table 1 Patient characteristics by dose of cranial radiation therapy (N = 48)

	12/12.6 Gy (n = 30)	18 Gy (n = 18)	P-Value
Median age at diagnosis, yr (range)	6 (1-14)	7 (2-13)	.637
Median age at radiation therapy, yr (range)	7 (2-14)	7 (3-13)	.646
Median initial height z_0 (range)	-0.55 (-2.2 to 1.4)	-0.85 (-3.1 to 0.8)	.654
Fraction size (Gy/Fraction)			$<.0001$
1.5	25 (82%)	2 (11%)	
1.8	5 (18%)	6 (33%)	
2.0	0	10 (56%)	
Sex			1
Male	20 (67%)	12 (67%)	
Female	10 (33%)	6 (33%)	
Race			.66
Hispanic	12 (40%)	10 (56%)	
White	8 (27%)	4 (22%)	
African-American	7 (23%)	2 (11%)	
Asian	3 (10%)	2 (11%)	
Histology			.70
Pre-B-Cell	10 (33%)	7 (39%)	
T-Cell*	20 (67%)	11 (61%)	
White blood cell count at diagnosis (cells/μL)			.31
$<50,000$	9 (29%)	8 (44%)	
$\geq 50,000$	21 (71%)	10 (56%)	
Median follow-up, yr (range)	4.9 (3.0-11.8)	6.0 (3.1-10.5)	.20

  * Includes T-Cell Lymphoma (1 in 12 Gy, 2 in 18 Gy).

Table 2 Univariate analysis of generalizing estimating equations model parameters for change in height z-scores (N = 48)

Parameter	Category	Estimate	95% Confidence Intervals	P-Value
Visit		−0.0208	(−0.0856 to 0.0439)	.5283
Race	African-American	0.0093	(−0.3167 to 0.3352)	.9556
	Asian	0.090	(−0.380 to 0.5602)	.7076
	Hispanic	−0.0076	(−0.2527 to 0.2375)	.9517
	White (reference)			
Histology	T-Cell	−0.1476	(−0.3734 to 0.0783)	.2004
	Pre-B-Cell (reference)			
Dose (Gy)	12/12.6	0.2374	(0.032-0.4428)	.0235*
	18 (reference)			
White blood cell count (cells/μL)	<50,000	−0.0559	(−0.283 to 0.1713)	.6299
	>50,000 (reference)			
Sex	Female	−0.0521	(−0.2994 to 0.1952)	.6798
	Male (reference)			
Fraction size (Gy/fraction)	1.5	0.0545	(−0.1664 to 0.2754)	.6287
	1.8/2.0 (reference)			
Age at radiation therapy (yr)		−0.0297	(−0.0595 to 0.0001)	.0505

*P < .05.

and boys (Fig 2) with positive growth seen in patients who received 12 Gy at all 3 time points. Changes in weight or BMI z-scores were not statistically significant between the dose levels in either girls or boys.

The GEE model found that increasing age at the time of RT was a statistically significant parameter, with each yearly increase in age leading to a 0.03 decrease in the average change in height z-scores. No statistically significant changes due to age were seen in change in weight or BMI z-scores.

Assessment of growth hormone deficiency

Cranial RT has been shown previously to affect the pituitary axis and possibly to induce GH deficiency (GHD). In this cohort, routine testing for GH using stimulation tests was not regularly performed. As a surrogate for concern for GHD testing, the frequency of serum GH testing, clinical endocrinology referrals, and GH supplementation were compared. There was no statistically significant difference in the frequency of testing for serum GH markers (either insulin-like growth factor-1 or insulin-like growth factor binding protein-3; 20% vs 22%, P = 1) or referrals to the pediatric endocrinology clinic (10% vs 17%, P = .66). Furthermore, none of the patients in the cohort received GH supplementation during the study period.

Discussion

Clinical science has progressed to make pediatric ALL a highly curable disease, with some groups advocating omitting cranial RT out of concern for long-term toxicities such as growth impairment, cognitive deficits, and secondary malignancies. In our study, children who received 12 Gy were able to maintain normal growth curves for height (change in z-score ≥0) for at least the 3 years immediately after cranial RT. In comparison, children who received 18 Gy experienced stunting of growth (change in height z-score <0) as early as the first year post-RT. Given these findings and with further follow-up, this may lead to significant changes in final adult height.

A previous study[23] has suggested that treatment for ALL leads to increased weight and BMI, but the authors' attribute this effect to both corticosteroids and nutrition

Table 3 Multivariable generalizing estimating equations model estimates for change in height z-scores (N = 48)

| Parameter	Category	Estimate	95% Confidence Intervals	P-Value
Visit		−0.0208	(−0.0856 to 0.0439)	.5283
Dose (Gy)	12/12.6	0.252	(0.0624-0.4415)	.0092*
	18 (reference)			
Sex	Female	−0.1167	(−0.3218 to 0.0884)	.2648
	Male (reference)			
Age at radiation therapy (yr)		−0.0345	(−0.0637 to −0.0052)	.0211*

*P < .05.
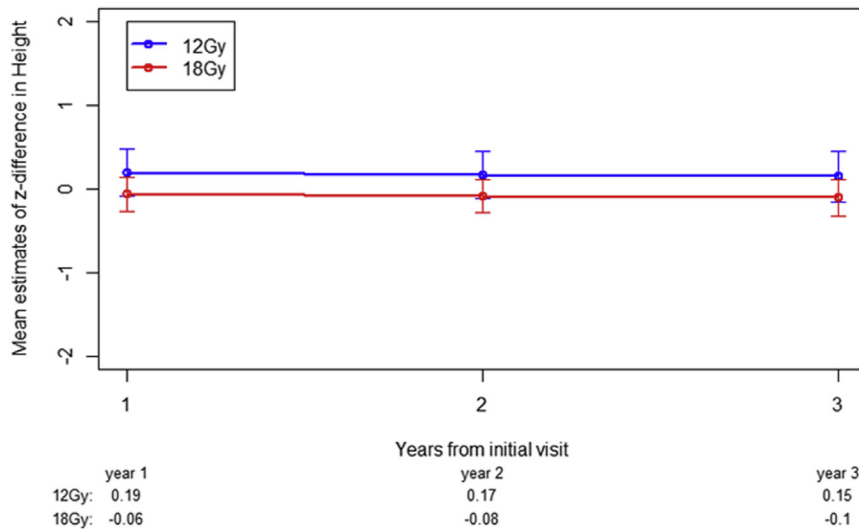
Figure 1   Effect of cranial radiation therapy dose on change in height from initial visit, by dose.

because most of the patients lost weight during treatment. However, in this study, we did not find an association between either 12 Gy or 18 Gy and increased weight or BMI. Another study showed that while the largest period of increase for BMI was from before the diagnosis until the end of therapy, patients who received RT had a significant increase in BMI (z-score = .61) once they reached their final height.[24] Our study only followed patients in the first 3 years after RT, and further follow-up is needed to see if there is an effect on BMI once final height is reached.

The other important factor associated with height impairment is the initial age at the time of radiation treatment. In this study, older age was associated with a very slight decrease in height. This may be due to sensitivity of the second musculoskeletal growth phase just before puberty.[25] This study excluded patients who were <2 years old and many older female patients who had already undergone menarche, making it less comparable to prior studies that compared patients aged 0 years to 13+ years, which showed a more significant decrease in height z-score with patients of a younger age.[23] Furthermore, this study only looked at the first 3 years post-radiation, and further follow-up could elucidate the effect of younger age on final adult height.

Despite the clinical observation of height impairment with cranial radiation, the mechanism for this blunted growth is not well understood. There is a dose-response
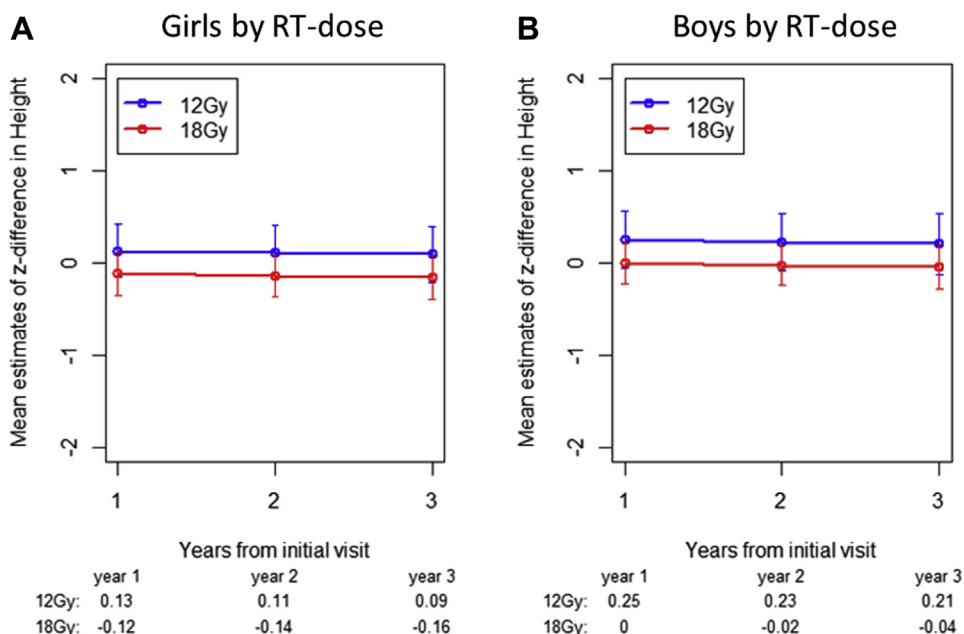
Figure 2   Effect of cranial radiation therapy dose on change in height from initial visit by dose in (A) girls and (B) boys.

relationship of height with hypothalamus RT doses, with the smallest effect when the hypothalamus is irradiated at doses ≤20 Gy.[26] However, case series have showed that patients who receive 18 to 25 Gy of cranial RT can have growth abnormalities, including 2 patients with hypothyroidism and 4 with gonadal failure with alterations in GH secretion noted.[27] Our study shows that the 18 Gy dose was sufficient to induce height impairment, although it is unclear if these is due solely to GHD, which may require more than 3 years to manifest. We were unable to detect any patients with documented GH deficiency, and the number of patients who had clinical suspicion (based on serum testing and/or referral to specialists) did not differ between groups, which makes it difficult to determine the mechanism of this height difference without more widespread testing of GHD.

This study has some limitations. This is a retrospective, single-institutional study and suffers from biases that are associated with this type of analysis. Patients were not randomized to receive 12 or 18 Gy, and given the limited follow-up, patients may not have reached their final adult height. Furthermore, many patients who received 18 Gy had more disease burden because many of them had CNS3 disease, which necessitated treatment with more intensive chemotherapy that could be a possible confounder.

Finally, studies have investigated the effect of using chemotherapy alone for CNS prophylaxis and whether height impairment is seen. In one study of patients treated with chemotherapy alone, height decreased and BMI increased during treatment. This growth change persisted in girls until the last follow-up and suggests that chemotherapy alone may affect GH levels.[28] In contrast, another study showed normal final height after treatment in patients who received chemotherapy alone, with an initial median height z-score at diagnosis of −0.01 and a final median height z-score of −0.035.[29] An important question remains: whether 12 Gy cranial RT has a similar effect on height impairment compared with a matched cohort of patients who received only chemotherapy, which will be the subject of a future study.

The findings of this study show that 12 Gy is associated with normal growth when compared with 18 Gy cranial RT. This is the first study to compare a lower cranial RT dose level (12 Gy) to the common standard (18 Gy) and its effect on height and weight indices. This study suggests that height impairment with cranial RT can be minimized with a lower RT dose.

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