A Retrospective Study of the Effects of Craniospinal Irradiation (CSI) on Height in Children with Brain Tumor

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ABSTRACT

Objective: To compare height standard deviation score (SDS) at start of radiation therapy and at the last follow-up in children with brain tumor treated with CSI.

Methods: This study is a retrospective study. Medical records of children aged 3-15 years old, diagnosed with embryonal or germ cell tumor, and treated with 3D conformal radiation therapy (3DCRT) for CSI at Division of Radiation Oncology, Siriraj Hospital between 2006 and 2014 were reviewed. Patient's demographic data, clinical information, radiotherapy technique, weight and height before the start of radiation therapy and at follow-up were obtained. The height standard deviation score (SDS) was calculated by INMU-Nutri Stat software program.

Results: There were twenty one eligible patients. Overall, the latest height SDS was significantly reduced. Mean reduction of the height SDS was 1.24 ± 1.08 ($p < 0.001$). Four patients (19%) had the latest height SDS < -2. Positive correlation between initial height and the latest height ($p = 0.001$), and negative correlation between hypothalamic-pituitary axis (HPA) mean dose and the latest height ($p = 0.02$) were found. The patients who received HPA mean dose more than 47Gy tended to have the latest height SDS less than -1.5.

Conclusion: Children treated with CSI have significant reduction of height even 3D-CRT was used. The incidence of short stature is 19%. The initial height is strongly related to the latest height. Weak negative correlation of radiation dose to HPA and the latest height was observed.

Keywords: Craniospinal irradiation; growth height; medulloblastoma; germ cell tumor (Siriraj Med J 2018;70: 343-348)

INTRODUCTION

Craniospinal irradiation (CSI) is standard treatment for childhood brain tumors with neuraxis dissemination or with high propensity of neuraxis dissemination, including most embryonal tumors and some germ cell tumors. Embryonal tumors include medulloblastoma (MB), supratentorial primitive neuroectodermal tumor (sPNET), atypical teratoid/rhabdoid tumor (AT/RT), pineoblastoma, and others. Both embryonal tumors and germ cell tumors are treated with combined modality approaches: surgery, radiation therapy (RT), and chemotherapy. The side effects attributed to radiation is of primary concern for patient with brain tumor treated with CSI. Due to prolonged survival, late complications affecting quality of life have been observed including short stature and endocrine dysfunction.[1-4] Reduced adult height in survivors is caused mainly by three factors: growth hormone deficit, early puberty, and impaired spinal growth.[1] All of these factors can be induced by CSI. Therefore, this study was conducted to compare height standard deviation score (SDS) at start of radiation therapy and at the last follow-up in children with brain tumor treated with CSI.

MATERIALS AND METHODS

Patient selection

All children diagnosed with brain tumor treated with 3D conformal radiation therapy (3DCRT) for CSI at Division of Radiation Oncology, Department of Radiology,

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Faculty of Medicine Siriraj Hospital between 2006 and 2014 were identified via the radiation oncology database for retrospective analysis after institutional review board approval (Si 606/2016). Inclusion criteria were as follows: (1) histological confirmed embryonal tumors or germ cell tumors (2) age > 3 years and ≤ 15 years at start radiation therapy (3) receiving craniospinal radiation therapy via 3-DCRT. Patients who have been followed-up less than 2 years and/or no weight and height measuring before start radiation therapy and once a year during follow-up were excluded.

Radiotherapy

Prescribed dose and target volumes for craniospinal radiation therapy and boost volume were obtained from patient chart and the online patient database.

Planning and evaluation

The dose-volume histograms (DVH) of the treatment targets and normal structures were evaluated from computer based planning system.

Follow-up

Assessments for weight and height measurement before and after completion of radiation therapy were obtained from patient chart and the online patient database.

Outcome variable and assessment

The primary endpoint for this study was height SDS at the last follow-up. Height SDS was calculated with age-matched mean value in the normal Thai population, and evaluated with INMU-Nutri Stat software program. Height SDS was categorized according to INMU-NutriStat software program, as follows: SDS < -2 SD corresponds to short stature, SDS between -1.5 SD to -2 SD corresponds to relatively short stature, SDS between -1.5 SD to 1.5 SD corresponds to normal stature, SDS between 1.5 SD to 2 SD corresponds to relatively tall stature, and SDS > 2 SD corresponds to tall stature. Loss of height was the difference between the initial height SDS (height SDS before start radiation therapy) and the latest height SDS (height SDS at the last follow-up).

Statistical analysis

All analyses were performed using STATA version 14.2. Data were presented by descriptive methods (frequency, percentage, mean ± SD). In addition, the independent-sample t-test and Mann-Whitney *U* test were used to compare the latest height SDS to the initial height SDS. Multivariable linear regression analysis was performed to evaluate the effect of potential risk factors on the latest height. All statistical analyses were two-sided with significance defined as a *P*-value < 0.05.

RESULTS

Patient demographics

Patient demographics and clinical information are shown in Table 1. Thirty four patients were included. Thirteen patients were excluded due to incomplete data or less than 2 years available follow-up data. Mean age at start of radiation therapy was 10.11 ± 3.68 years. Embryonal tumors were classified into two groups; average and high risk groups. The average risk group included patients with all of the following characteristics; were aged ≥ 3 years at diagnosis, had M0 disease, and underwent gross total tumor removal (GTR). Other patients and patient with sPNET were categorized as being in the high risk group.

Growth height

The data for each patient is detailed in Table 2. The mean initial height SDS was 0.09 ± 1.3. The mean latest height SDS was -1.15 ± 1.30. There were 4 patients (19%) with the latest height SDS < -2 and 8 patients (38.1%) with the latest height SDS < -1.5. Overall, the latest height SDS was significantly reduced. Mean loss of height SDS was 1.24 ± 1.08 (P < 0.001).

Three patients (14.3%) received growth hormone replacement therapy (GHRT). All who received GHRT have the latest height SDS > -2 (Table 3).

Multivariable risk factor analysis

The potential risk factors include sex, age at start radiation therapy, initial height SDS, vertebral mean dose, and hypothalamic-pituitary axis (HPA) mean dose. Linear regression analysis showed significant effect of initial height SDS and HPA mean dose on the latest height (Table 4). Their relations were shown in Figs 1 and 2. Patients with HPA mean dose more than 47Gy trended to have the latest height SDS less than -1.5 (Fig 2).

DISCUSSION

Decrease in the final height in children treated with radiation therapy has been observed for a long time, especially in children treated with cranial irradiation or craniospinal irradiation.[5-14] In our study, all children were treated CSI with 3D-CRT. The results were similar to recent data from Japan, using conventional radiation therapy and 3D-CRT. Odagiri K et al., found that 35% of children treated with CSI have the latest height SDS less than -2. In their study, 4 children had failure to

TABLE 1. Demographic and clinical information.

Diagnosis	Patient No.	Sex	Primary site	M stage	Extent of surgery	Age at start RT (years)	CSI dose (Gy)	Boost dose (Gy)
sPNET	1	F	S	M0	GTR	4.67	23.3	54
MB (average risk)	2	F	I	M0	GTR	8.92	23.4	54
	3	M	I	M0	GTR	9.5	23.4	54
	4	F	I	M0	GTR	10.83	36	55.8
	5	M	I	M0	GTR	4.08	30.6	50.4
MB (high risk)	6	M	I	M1	STR	13.5	36	55.8
	7	M	I	M4	GTR	7.92	36	55.8
	8	M	I	M1	STR	12	23.4	54
	9	F	I	M4	GTR	3.33	36	54
	10	M	I	M1	GTR	5.75	36	55.8
	11	M	I	M1	GTR	11.08	36	55.8
	12	F	I	M3	STR	5.33	36	55.8
Pure germinoma	13	M	P	-	Biopsy	14.08	36	54
	14	M	BG	-	Biopsy	13.67	21.6	36
NGGCT	15	M	BG	-	Biopsy	11.75	36	54
	16	M	P	-	Biopsy	13.42	24	36
	17	M	P	-	STR	14.08	40	54
	18	M	P	-	Biopsy	14.25	36	54
	19	M	SS	-	Biopsy	12.33	36	50.4
	20	M	SS	-	STR	8.5	36	54
	21	M	BG	-	STR	13.42	36	54

Abbreviations: sPNET=supratentorial primitive neuroectodermal tumor, MB=medulloblastoma, NGGCT=nongerminomatous germ cell tumors, F=female, M=male, S=supratentorial, I=infratentorial, P=pineal, BG=basal ganglia, SS=suprasellar, STR=subtotal tumor removal, GTR=gross total tumor removal, RT=radiation therapy, CSI=craniospinal irradiation

control disease, all of those children had the latest height SDS < -2. When these children were removed from the study group, only 15% of children had short stature. They also found that dose of CSI and age at start of RT has no effect on height or loss of height.[15]

Major causes of short stature in children treated with CSI are growth hormone deficiency, spinal bone growth arrest, and early puberty.[10,16-21] Cranial RT can induce the dysfunction of the HPA, resulting in disruption of growth hormone, followed by gonadal, adrenal, and thyroid hormones. These multiple hormone deficiencies lead to abnormal growth and puberty.[22] Furthermore, spinal irradiation has the additional effect on spinal bone growth. Shalet SM et al., found that spinal irradiation has a profound effect on spinal bone growth. The greater subsequent skeletal disproportion was associated with younger age at receiving CSI.[20]

More conformal radiation therapy technique in our study, 3D-CRT, has failed to reduce the incidence of short stature in children who have received CSI. The growth hormone deficiency (GHD) could develop even in those who received a dose as low as 10 Gy to the HPA.[22] The spinal growth retardation can be induced from CSI with a dose as low as 25 Gy.[23] Photon cannot avoid dose to HPA and vertebral bodies, so the late effect on height is still observed.

TABLE 2. Treatment related information and height.

Diagnosis	Patient No.	VB mean dose (Gy)	HPA mean dose (Gy)	GH	Age at the latest assessment (years)	Initial Height (SDS)	Latest height (SDS)
sPNET	1	36.2	37	No	8.75	0.12	0.02
MB (average risk)	2	24.7	26	No	12.75	0.22	-1.94
	3	24.1	24.3	No	12.25	-0.65	-1.39
	4	35	37	No	18.92	1.23	0.6
	5	29.8	30.5	Yes	12.5	-0.75	-1.84
MB (high risk)	6	37.2	38	No	16.58	2.83	1.18
	7	37.7	37.5	No	12.5	-1.03	-0.69
	8	22.8	24.3	No	17.5	0.18	-0.78
	9	37.1	37.4	No	5.75	0.41	-2.04
	10	37.8	38.7	Yes	11.83	0.22	0.16
	11	36.2	36.9	No	17.42	-1.65	-3.19
	12	34	37	Yes	13.5	1.15	-0.98
Pure germinoma	13	42.2	44.4	No	19.67	-0.4	-1.64
	14	21.1	35.6	No	19.83	0.12	-1.45
NGGCT	15	35.3	48.9	No	17.83	1.36	-1.92
	16	24.6	28.5	No	18.58	-1.15	0.21
	17	37.7	46.5	No	19.92	1.54	0.38
	18	34.8	36.7	No	16.17	-0.6	-1.33
	19	30.3	52.4	No	16	1.61	-1.06
	20	38.8	54.4	No	13.58	-2.73	-4.26
	21	35.1	50.8	No	18.58	-0.08	-2.09

Abbreviations: sPNET=supratentorial primitive neuroectodermal tumor, MB=medulloblastoma, NGGCT=nongerminomatous germ cell tumors,VB=vertebral bodies, HPA=hypothalamic-pituitary axis, GH=growth hormone replacement, SDS=standard deviation score

TABLE 3. Translation of height SDS in 3 patients treated with GHRT.

Patient no.	Height SDS (age)		
	At start RT	At start of GHRT	At the last assessment
5	-0.75 (4.08)	-2.48 (10.25)	-1.84 (12.5)
10	0.22 (5.75)	0.16 (11.83)	0.16 (11.83)
12	1.15 (5.33)	-0.93 (12.58)	-0.98 (13.5)

Abbreviations: GHRT=growth hormone replacement therapy, SDS=standard deviation score

TABLE 4. Multivariable linear regression analysis of risk factors for the latest height.

Risk factor	Coef.	(95% CI)	P-value
Sex	0.38	(-0.99 to 1.75)	0.56
Age at start RT	0.04	(-0.12 to 0.20)	0.57
Initial height SDS	0.72	(0.33 to 1.12)	0.001
VB mean dose	0.07	(-0.03 to 0.18)	0.14
HPA mean dose	-0.09	(-0.16 to -0.02)	0.02

Abbreviations: Coef.=Coefficient, CI=confidence interval, RT=radiation therapy, SDS=standard deviation score, VB=vertebral, HPA=hypothalamic-pituitary axis

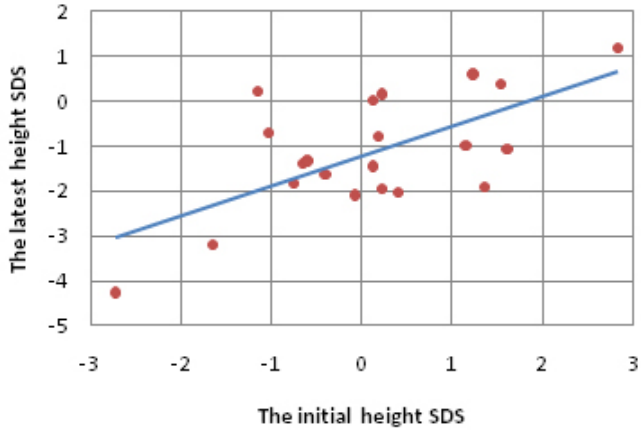

Fig 1. Scatter plot and the regression line (blue line) show positive relation between the initial height SDS and the latest height SDS.

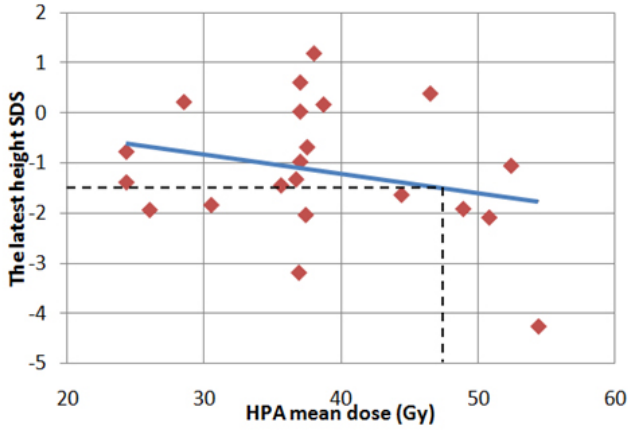

Fig 2. Scatter plot and the regression line (blue line) show negative relation between HPA mean dose (Gy) and the latest height SDS. HPA mean dose greater than 47 Gy is related to the latest height SDS less than -1.5.

Proton, the particle beam therapy which is highly precise to target and has rapid dose fall-off, has now published the role of limited dose to organs at risk to reduce radiation acute and late side effects including height. Eaton B.R. et al., found that children treated by CSI with proton achieve a greater height SDS than those with photon (-1.19 ± 1.22 vs. -2 ± 1.35) without significant difference in the incidence of GHD (53% vs. 57%).Their study also included whole vertebral bodies in CSI treatment volume, dose range 18-27 Gy. No dose to HPA was reported.[24]

In our exploratory analysis we found that the initial height and dose to HPA are related to the latest height. Dose to HPA greater than 47 Gy is associated with the latest height SDS less than -1.5. However, this observation is not strong enough to encourage the dose limitation to HPA due to the weak association. More supporting data is still needed.

Our study cannot evaluate the adult final height SDS because most children were aged under 18 years at the last follow-up. We only could report the latest height SDS. This major weakness was related to the retrospective nature of our study.

CONCLUSION

Children treated with CSI have significant loss of height even though 3D-CRT was used. The incidence of short stature is 19%. The initial height is strongly related to the latest height. Weak negative relation of dose to HPA related to the latest height was observed

Conflicts of Interest: The authors have declared no conflicts of interest.

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