

The evaluation of dose distribution of vertebral growth plates in pediatric patients who underwent craniospinal radiotherapy

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Abstract

Aim: The aim of this study was to evaluate the suitability of the dose distribution of vertebral growth plates in pediatric patients undergoing craniospinal radiotherapy with the recommendations of the SIOPE radiotherapy study group.

Material and Methods: The study included 20 patients under the age of 12 who underwent 3-dimensional conformal craniospinal radiotherapy. For each patient, posterior and anterior primary ossification center of the cervical, thoracic, lumbar and sacral vertebrae regions were re-contoured. The mean doses of each primary ossification center were determined and then the gradients were determined. The difference between the average doses of the anterior and posterior ossification centers of the vertebrae was evaluated separately for the cervical, thoracic, lumbar and sacral regions. Data were analyzed with descriptive statistics.

Results: The mean doses of the posterior and anterior primary ossification center were respectively 23.62 Gy and 22.54 Gy for those lower than 25 Gy and 34.06 Gy and 33.09 Gy for those who underwent a dose greater than 25 Gy. The dose differences of the anterior and posterior ossification centers in the cervical, thoracic, lumbar and sacral vertebrae is lower than 5 Gy for those who underwent lower dose than 25 Gy.

Conclusion: The planning data of craniospinal radiotherapy, which is applied to the cranial region with two lateral fields and the spinal area with single field, complies with the SIOPE recommendations.

Primary and secondary ossification centers should be identified as the organ at risk for radiotherapy planning in the pediatric group undergoing craniospinal radiotherapy.

Keywords: CSRT; vertebral primary ossification centers; radiotherapy dose distribution.

INTRODUCTION

Craniospinal radiotherapy (CSRT) is an essential part of treatment in pediatric central nervous system (CNS) tumors (medulloblastoma, atypical teratoid rhabdoid tumor, ependymoma, germinoma) with a high risk of spinal spread. CSRT is applied to a very large area, that covering the entire brain and spinal region. While a high dose of 54 Gy is administered to the primary disease site, doses ranging from 20 to 40 Gy are administered to the entire spinal region according to the risk group (1). Today, despite the use of CSRT with the treatment of normal tissue with less irradiation of the target tissue, such as conformal radiotherapy, intensity-modulated radiotherapy, and proton therapy, the treatment still has significant side effects, including long-term serious sequelae.

In addition to neurological and hematological complications after CSRT, normal growth and development is impaired in patients. Short stature in children who underwent CSRT prior to pubertal period is an expected complication of treatment and associated chemotherapy increases the severity of shortness (2,3). Endocrine monitoring and hormone replacement, if necessary, are performed to reduce growth retardation after CSRT. In addition to short stature, spinal problems such as kyphoscoliosis develop in this patient group in the long term. To achieve homogeneous dose distribution in vertebrae during CSRT planning phase, it can reduce asymmetric growth problems such as kyphosis, lordosis, scoliosis that may occur during the growth and development of vertebrae, hypoplasia and secondary respiratory distress due to deformed growth of thoracic spina.

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SIOPE radiotherapy working group has published a review in which it recommends to avoid inhomogeneity in pediatric patients who have undergone radiotherapy to the vertebral region. In this review, acceptable dose gradients in the vertebrae for different age groups in craniospinal and paravertebral radiotherapy applications have been defined (4).

In this study, we aimed to evaluate the compliance of SIOPE radiotherapy study group with the recommendations of the craniospinal dose distribution by retrospectively examining the planning data of a group of patients undergoing CSRT for medulloblastoma

MATERIAL and METHODS

Twenty patients with medulloblastoma among 79 patients who underwent 3-dimensional conformal craniospinal radiotherapy in our clinic were randomly selected from the database. The study included 20 patients under the age of 12 who underwent 3-dimensional conformal craniospinal radiotherapy. 10 of the patients were selected from the patients who received less than 25 Gy doses, while the other 10 patients were selected from the patients who received doses above 25 Gy. The 3-dimensional conformal craniospinal radiotherapy plans of the patients were used for evaluation. All patients had thermoplastic masks for immobilization. Six of the patients were immobilized in prone position. All of the patients were treated with three-dimensional (3D) RT which was applied to the cranial region with 2 lateral fields and the spinal area with single field.

The SIOPE radiotherapy study group recommended dose gradient for craniospinal irradiation for 1.8-2 Gy fractions per day; If the prescribed dose is 25 Gy or less, the posterior and anterior gradient should be less than 5 G, if doses greater than 25 Gy are to be administered, 20 Gy or more should include vertebra primary ossification centers (POC) (4). For each patient, posterior and anterior primary ossification center of the cervical, thoracic, lumbar and sacral vertebrae regions were re-contoured (Figure 1)

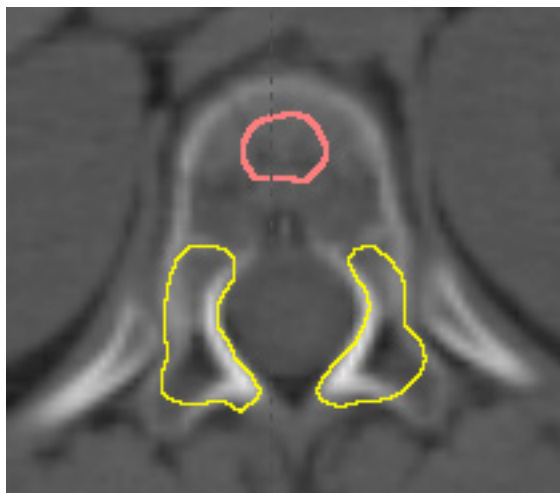


Figure 1. Thoracic vertebrae anterior primary ossification zone (pink) and posterior primary ossification zone (yellow)

The mean doses of each primary ossification center were determined and then the gradients were determined. The difference between the average doses of the anterior and posterior ossification centers of the vertebrae was evaluated separately for the cervical, thoracic, lumbar and sacral regions. Data were analyzed with descriptive statistics.

RESULTS

At the time of radiotherapy, the median age was 5.5 years; 10 patients were younger than 6 years and 10 patients were between 6 and 12 years old. All patients were treated with 3-dimensional conformal craniospinal radiotherapy with a fraction dose of 1.8 Gy. The median spinal dose was 27 Gy. Ten of the patients received doses of less than 25 Gy (mean 23.4 Gy), while others received doses between 30.6 Gy and 39.6 Gy (mean 35.28 Gy). The mean doses of posterior and anterior POC were 23.62 Gy and 22.54 Gy for patients who underwent dose under 25 Gy and 34.06 Gy and 33.09 Gy for patients who underwent dose above 25 Gy. The dose difference of the anterior and posterior ossification centers in the cervical, thoracic, lumbar and sacral vertebrae was less than 5 Gy for patients who underwent dose under 25 Gy. In our patient group, ossification centers received a dose of more than 20 Gy at all vertebrae levels of 10 patients who received a dose over 25 Gy and the minimum dose was 21.16 Gy. Table 1 and 2 show the difference in gradient according to the vertebrae level in those given a dose of less than 25 Gy and greater than 25 Gy and Table 3 shows the mean dose of anterior and posterior POC in patients receiving a dose greater than 25 Gy, respectively. whereas INR and TF were the most significant predictors of the APACHE II scores in the AMT group ($\beta=0.60$, $p<0.001$; and $\beta=0.42$, $p=0.001$, respectively).

Table 1. Gradient difference between posterior and anterior POC in patients less than 25 Gy

VERTEBRAE REGION	< 25 Gy (n = 10) (mean \pm SS)
Cervical	0.79 \pm 0.39 (0.26 – 1.32)
Thoracal	1.78 \pm 0.84 (0.58 – 3.57)
Lumber	1.49 \pm 0.61 (0.69 – 2.37)
Sacrum	1.44 \pm 0.68 (0.56 – 3.08)

Table 2. Gradient difference between posterior and anterior POC in patients greater than 25 Gy

VERTEBRAE REGION	> 25 Gy (n = 10) (mean ± SS)
Cervical	1.47 ± 0.71 (0.36 – 2.30)
Thoracal	3.25 ± 0.79 (2.32 – 4.44)
Lumber	3.11 ± 0.79 (2.10 – 4.34)
Sacrum	2.13 ± 0.9 (1.18 – 4.28)

Table 3. Mean doses of anterior and posterior POC in patients given a dose greater than 25 Gy

VERTEBRAE REGION	Anterior (n = 10) (mean ± SS)	Posterior (n = 10) (mean ± SS)
Cervical	36.52 ± 5.31 (29.81 – 43.33)	37.99 ± 5.09 (30.45 – 44.12)
Thoracal	34.15 ± 4.27 (37.96 – 39.41)	37.41 ± 4.85 (30.28 – 43.29)
Lumber	32.35 ± 4.03 (26.75 -37.34)	35.46 ± 4.56 (39.65 -41.40)
Sacrum	29.35 ± 5.27 (21.16- 35.48)	30.70 ± 5.14 (22.58 – 38.30)

Patients were evaluated separately in two different groups between 3-6 years and 6-12 years. The gradient difference between the anterior and posterior POCs in children under 6 years of age and who received a dose less than 25 Gy was 1.24 Gy (0.61 Gy for cervical , 1.62 Gy for thoracal, 1.62 Gy for lumber, 1.12 Gy for sacrum), the mean dose of the posterior and anterior POCs was 34.99 Gy and 32.73 Gy who received a dose more than 25 Gy.

DISCUSSION

POC doses correlate with SIOPE recommendations in both cranial, that performed from two opposing fields, and spinal, which performed from single field, RT plans.

In this study, vertebrae separated into groups to evaluating POC's dose heterogeneity. For reason, thoracic vertebrae contributes %30 of sitting height, while lumbar vertebrae %18 (5). Whereas, POCs were not grouped into left and right, because of performing single field RT for spinal region and symmetrical dose distribution at the dorsal part of vertebral bodies.

Vertebral growth rate varies according to age. The highest growth speed observes at 0-5 years old and puberty (6,7). Beside the RT dependent growth disturbances at 0-5 years-old age group, secondary muscle atrophy especially seen in lumbar region due to the RT ends up with serious spinal deformities. Due to fact that, muscles and soft tissues at lumbar region contoured as organ at risk (OAR) for children under 6 years old. Mean dose was above 25 Gy for lumbar muscles. Spinal irradiation performed from single field on the back of patient. So, mean dose of

lumbar muscles was lesser than target volume and POC (Mean dose 30.45 Gy). 2D RT techniques applied with Co 60 that used before 1980-1990s, may cause exposure of lumbar muscles to higher doses as much as create growth problems. Currently, preserving of skin, soft tissue and lumbar muscles are more available with modern RT techniques depending on photon energy. Although, our data are correlated with SIOPE guidelines, volumetric arc or proton therapy is recommended (4)

Fraction dose is another factor that can affects vertebral growth beyond the total RT dose and child's age. In this study, daily fraction dose was 1.8 Gy. The effect of fraction dose on vertebral body growth still remains unclear in the literature. Animal experiments showed detrimental effects of hypofractionated regimen on spinal development in comparison with conventional regimen. On the other hand, randomized PNET4 trial reported negative effect of hyperfractionated regimens (8,9).

Growth retardation is not caused only by physical effects of CRT on vertebrae. Also, hypothalamic-hypophyseal axis is deteriorated in course of cranial RT. All the hypophyseal hormones are affected above 20 Gy RT dose, however growth hormone insufficiency is the most frequent. Mean hypophysis dose was 38.71 Gy in 20 patients. According to this data, growth hormone insufficiency incidence is %40 in 5 years (10). Also, the other factors like chemotherapy, surgery, steroid use effect vertebral development.

General tendency is reducing the RT doses in pediatric tumors as much as we can. In trial SIOP PNET 5 MB (NCT02066220) , that is still ongoing, spinal dose reduced to 18 Gy in low risk group of patients with positive WNT. In the future, within the parallel of that study, growth plaques will be protected without losing local control at least in low risk group (11).

CONCLUSION

POC doses correlate with SIOPE recommendations in both cranial, that performed from 2 opposing fields, and spinal that performed from single field, RT plans. Primary and secondary ossification centers should be contoured as OARs in pediatric patients who undergo CRT. Beside the POC, lumbar muscles also should be considered for children especially who are less than 6 years old for preventing abnormal vertebral growth. After the RT, hormonal follow-up and hormonal replacement in case of necessity have critical importance for preventing developmental problems at early stage.

Competing interests: The authors declare that they have no competing interest.

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