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Scientific Article

Comparison of Craniospinal Irradiation Using Proton Beams According to Irradiation Method and Initial Experience Treating Pediatric Patients

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Purpose: This study compared craniospinal irradiation using proton beam therapy (PBT) according to irradiation method and investigated the initial effects.

Methods and Materials: Twenty-four pediatric patients (1-24 years old) who received proton craniospinal irradiation were examined. Passive scattered PBT (PSPT) and intensity modulated PBT (IMPT) were used in 8 and 16 patients, respectively. The whole vertebral body technique was used for 13 patients <10 years old, and the vertebral body sparing (VBS) technique was used for the remaining 11 patients aged ≥10 years. The follow-up period was 17 to 44 (median, 27) months. Organ-at-risk and planning target volume (PTV) doses and other clinical data were examined.

Results: The maximum lens dose using IMPT was lower than that using PSPT ($P = .008$). The mean thyroid, lung, esophagus, and kidney doses were lower in patients treated using the VBS technique compared with the whole vertebral body technique (all $P < .001$). The minimum PTV dose of IMPT was higher than that of PSPT ($P = .01$). The inhomogeneity index of IMPT was lower than that of PSPT ($P = .004$).

Conclusions: IMPT is better than PSPT at reducing the dose to the lens. The VBS technique can decrease the doses to neck-chest-abdomen organs. The PTV coverage of IMPT is superior to that of PSPT.

Introduction

Craniospinal irradiation (CSI) is the standard treatment for pediatric patients with tumors prone to leptomeningeal dissemination, such as medulloblastoma and some germ cell tumors.[1,2] Owing to the large field size, a significant volume of normal organs must be included in the irradiated area.[3] Therefore, various adverse effects, including hematologic and gastrointestinal toxicities, can be observed during and after CSI.[4-8] In an effort to reduce the potential toxicities related to CSI, advanced techniques have been adopted. Among these, proton beam therapy (PBT) has received attention because of its dosimetric advantage.[9,10] In contrast to

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photon radiation therapy (RT), PBT involves a sharp rise and fall in energy deposition, known as the Bragg peak; the physical features of the Bragg peak result in energy deposition ending within a finite beam range.[11] Therefore, PBT can reduce unnecessary doses to the neck, chest, and abdominal organs,[11-13] and fewer acute and late adverse effects are expected after PBT compared with photon RT.

Techniques for the delivery of PBT have advanced in recent decades. One of the most representative advances is the development of the spot scanning technique using pencil beams.[14] In the spot scanning irradiation technique, a lesion is visualized as a mass of points, and each point is irradiated individually; this approach contrasts with conventional passive-scattered broad beam irradiation, in which a bundle of proton beams shaped to match the lesion is used. Scanning PBT is associated with superior beam flexibility, allowing adaptation to complex-shaped targets. Superior target coverage can easily be attained, and techniques such as intensity modulated PBT (IMPT) can further reduce normal tissue irradiation compared with passive scattered PBT (PSPT). Other advantages are a reduced manufacturing cost for patient-specific apertures or compensators and a reduced time required to change the devices during delivery.[15,16] The number of facilities offering IMPT is growing rapidly worldwide. IMPT is expected to be advantageous for the treatment of CSI because of the normal tissue dose reduction and target dose robustness, but its actual effectiveness has only been discussed in a few papers describing a very small number of patients (less than 10)[17-19] because of the small number of patients requiring CSI at most proton beam facilities and the few facilities that can perform this therapy. On a technical note, the vertebral body sparing (VBS) technique is recommended to avoid hematologic toxic effects. In contrast, the whole vertebral body (WVB) technique is usually used to avoid postural curvature. Most facilities select the VBS or WVB technique according to patient age.

Our facility was established in December 2017 and is adjacent to one of the largest regional hospitals for pediatric cancer in Japan. The number of pediatric patients receiving PBT at our facility has been the highest in Japan since 2018. We have already used proton CSI to treat more than 20 patients, as discussed in a previous study.[20] In the present study, we compared different irradiation methods and reviewed our initial experience providing CSI using proton beams in a pediatric population treated at our facility.

Methods and Materials

All the study procedures involving human participants were conducted in accordance with the ethical standards of the institutional research committee, in compliance with the Declaration of Helsinki, and with the approval of the institutional review board (institutional approval no. 04-03). This study was conducted as a retrospective study, and we obtained patient consent via the opt-out method using the hospital's website.

The patients were 24 consecutive patients (1-24 years old; mean age, 10 years) with pediatric brain tumors who had completed CSI between February 2019 and March 2021. RayStation, version 7 or 9 (RaySearch Medical Laboratories, Stockholm, Sweden) was used for treatment planning. The clinical target volume (CTV) included the whole brain and spinal canal. Planning target volume (PTV) was defined using a 3-mm uniform expansion of the brain CTV and a 6-mm uniform expansion of the spinal cord CTV. The vertebrae was included in the PTV for the patients under the age of 10 years. For PSPT, the beam direction to the brain was 2 left-right contralateral beams in 6 patients and 2 oblique posterolateral beams in 2 patients; for IMPT, 2 oblique posterolateral beams were used in all the patients. The spinal cord was irradiated posteriorly in all the cases treated with PSPT or IMPT. To mitigate hot and cold spots at the field junction, 2 sets of plans with different field levels were used for PSPT. IMPT used overlapping field plans, which allowed field junctions to receive low-gradient doses so as to suppress hot and cold spots. Robust setting was 1% of range uncertainty to the PTV in the brain and 4 mm to the superior and inferior direction with 1% of range uncertainty to the PTV in the spinal cord levels.

We investigated the organ-at-risk (OAR) and PTV doses and other clinical data including hematologic toxicity during the treatment period. To evaluate the PTV dose, we calculated 4 parameters: the maximum dose (D_{max}), the minimum dose (D_{min}), the conformity index (CI), and the inhomogeneity index (INH). D_{max} and D_{min} were defined as dose of 1% and 99% of the PTV, respectively. The CI and INH were calculated as follows:

$$CI = \frac{PTV_{pre}}{PTV} \times \frac{PTV_{pre}}{V_{pre}}$$

$$INH = \frac{D_2 - D_{98}}{D_{pre}},$$

where PTV_{pre} is the PTV covered by the prescription dose, V_{pre} is the volume of the prescription isodose, D_2 and D_{98} are the doses to 2% and 98% of the PTV, and D_{pre} is the prescription dose.

For clinical and hematologic data, survival and recurrence were examined. Clinical endpoint was patients' death. Unpaired and paired *t* tests were used to compare the data between patient groups, and *P* values <.05 were considered statistically significant.

Results

The primary diseases were as follows: medulloblastoma, n = 18; germ cell tumors, n = 3; choroid plexus

tumor, n = 1; undifferentiated large cell lymphoma, n = 1; and glioma, n = 1. The treatment method was PSPT in 8 patients (February-October 2019) and IMPT in 16 patients (January 2020-March 2021). In the 8 patients who received PSPT, the WVB technique was used for 4 patients under the age of 10 years, with the vertebrae included in the PTV; the VBS technique was used for the remaining 4 patients who were 10 years or older. In the 16 patients who received IMPT, the WVB technique was used for 7 patients, and the VBS technique was used for the remaining 9 patients. The total CSI dose was 18 Gy (relative biologic effect [RBE]) in 3 patients, 23.4 Gy (RBE) in 17 patients, 25.2 Gy (RBE) in 2 patients, and 36 Gy (RBE) in 2 patients, with a daily administration of 1.8 Gy (RBE). Boost irradiation to the local region was performed in 23 of the 24 patients. Neoadjuvant and concurrent chemotherapy were performed in 23 and 20 patients, respectively. The follow-up period was 17 to 44 (median, 27) months as of December 2022 (Table 1).

OAR doses

The maximum dose to the lens using IMPT was lower than that using PSPT (7.9 ± 1.1 vs 10.5 ± 3.2, $P = .008$, Fig. 1). The maximum dose to the cochlea and the mean dose to the cochlea, thyroid, lungs, esophagus, and kidneys tended to be lower using IMPT without significance. When the WVB and VBS techniques were compared, the mean doses to the thyroid, lungs, esophagus, and kidneys were lower in the VBS groups (4.5 ± 2.6 vs 0.4 ± 0.4; 2.8 ± 0.9 vs 1.2 ± 0.7; 13.5 ± 3.3 vs 0.8 ± 0.9; and 3.3 ± 1.3 vs 0.6 ± 0.5, respectively; all $P < .001$; Fig. 2).

PTV dose

Using PSPT, the maximum and minimum PTV doses were 103.3% ± 0.9% and 90.8% ± 5.6% of the prescribed doses, respectively. The CI and INH were 0.46 ± 0.08 and 0.1 ± 0.03, respectively. Using IMPT, the maximum and minimum PTV doses were 103.6% ± 0.6% and 94.9% ±

Table 1 Patient summary

Age	**1-24 (10)**
Sex	Male: 17, female: 7
Disease	Medulloblastoma (n = 18)
	Germ cell tumors (n = 3)
	Choroid plexus tumor (n = 1)
	Undifferentiated large cell lymphoma (n = 1)
	Glioma (n = 1)
Combined therapy	Neoadjuvant surgery (n = 21)
	Neoadjuvant chemotherapy (n = 23)
	Concurrent chemotherapy (n = 20)
	Boost radiation therapy (n = 23)
Concurrent chemotherapy	CDDP + CPM containing (n = 14)
	Weekly VCR (n = 4)
	Others (n = 2)
Dose	18-36 (23.4) Gy (RBE)
PSPT (n = 8)	WVB (n = 4)
23.4-25.2 (23.4) Gy (RBE)	23.4 Gy (RBE)
	VBS (n = 4)
	23.4-25.2 (23.4) Gy (RBE)
IMPT (n = 16)	WVB (n = 7)
18-36 (23.4) Gy (RBE)	23.4-36 (23.4) Gy (RBE)
	VBS (n = 9)
	18-36 (23.4) Gy (RBE)

Abbreviations: CDDP = cisplatin; CPM = cyclophosphamide; IMPT = intensity modulated proton beam therapy; PSPT = passive scattered proton beam therapy; RBE = relative biological effect; VBS = vertebral body sparing; VCR = vincristine; WVB = whole vertebral body.
Numbers in parentheses are median values.

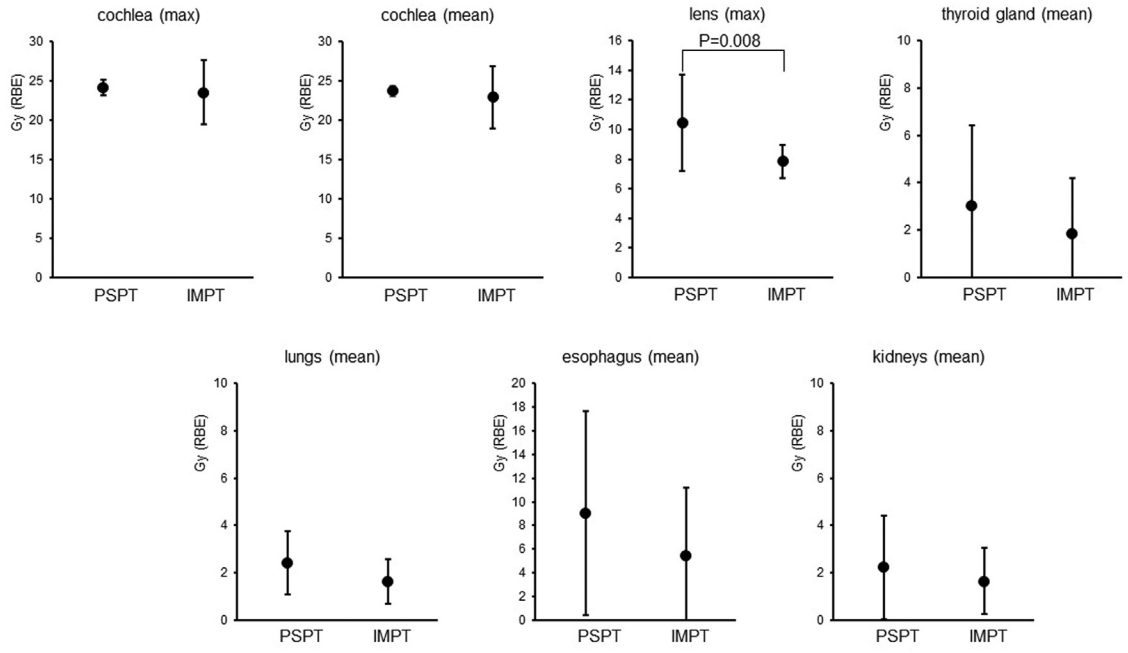

Figure 1 Comparison of organ-at-risk doses between passive scattered proton beam therapy (PSPT) and intensity modulated proton beam therapy (IMPT).

1.3%, respectively, and the CI and INH were 0.48 ± 0.08 and 0.07 ± 0.01, respectively. The minimum dose using IMPT was higher than that using PSPT (P = .01). The INH for IMPT was lower than that for PSPT (P = .004) (Table 2). No differences were found between the WVB and VBS techniques.

Toxicity

Blood sampling was conducted at the beginning and end of the CSI treatment or within 2 days. The red blood cell (RBC) and hemoglobin counts were reduced at the end of CSI treatment in the IMPT group (344.8 ± 49.7 vs

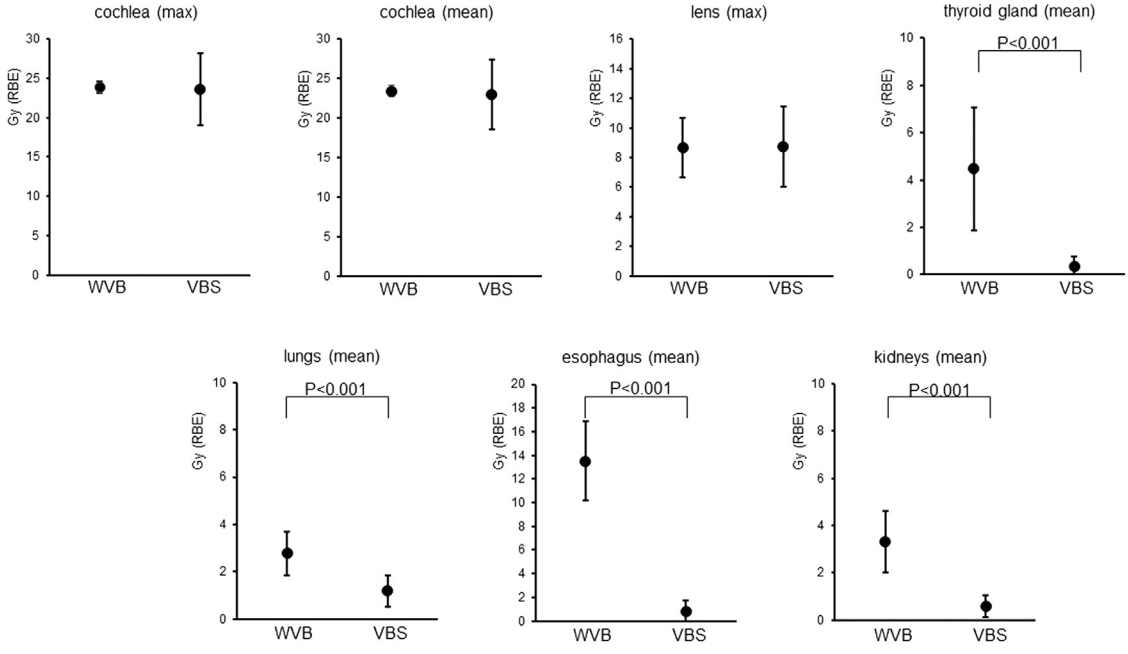

Figure 2 Comparison of organ-at-risk doses between whole vertebral body (WVB) and vertebral body sparing (VBS).

Table 2 Comparison of the PTV dose

	PSPT	IMPT	*P* value
Maximum	103.3 ± 0.9	103.6 ± 0.6	.31
Minimum	90.8 ± 5.6	94.9 ± 1.3	.01
CI	0.46 ± 0.08	0.48 ± 0.08	.49
INH	0.1 ± 0.03	0.07 ± 0.01	.004

Abbreviations: CI = conformity index; IMPT = intensity modulated proton beam therapy; INH = inhomogeneity index; PSPT = passive scattered proton beam therapy; PTV = planning target volume. Maximum and minimum values are percentiles of the prescription dose.

302.0 ± 48.0 [× $10^4/\mu$L], P = .01 and 9.8 ± 1.4 vs 8.8 ± 1.1 [g/dL], P = .04, respectively). However, the reduction in the platelet (PLT) mean value was more prominent in the PSPT group, and no consistent trend was observed for blood cells. When the WVB and VBS techniques were compared, the white blood cell (WBC) and RBC counts were reduced in the WVB group (71.8 ± 60.5 vs 29.2 ± 40.3 [× $10^2/\mu$L], P = .04 and 338.5 ± 32.0 vs 298.5 ± 59.2 [× $10^4/\mu$L], P = .046, respectively). The reductions in the mean values were more prominent in the WVB group than in the VBS group for all the examined blood cell counts (Fig. 3).

There were 12 cases of treatment-derived toxicity other than hematologic toxicity (PSPT: 4/8, IMPT: 9/16, WVB: 7/13, VBS: 6/11). Most often was hair loss in 7, followed by hearing loss in 5, and hypohormone production in 2, and so on.

Clinical course

Among the 8 patients who were treated with PSPT, recurrences occurred in 3 patients. Two recurrent patients were treated by RT and the remaining 1 patient was to be followed with the best supportive care. Seven patients were alive as of December 2022. Among the 16 patients who were treated with IMPT, a recurrence occurred in 1 patient. One recurrent patient was treated by RT. All the patients were alive as of December 2022.

Discussion

IMPT enables an increased dose conformity and increased degrees of freedom in dose-shaping capabilities. Giantsoudi et al[18] investigated a simulation study and revealed that the dose conformity of IMPT was better than that of PSPT, and a significant dose decrease was observed in the esophagus. In a similar study, Balasubramanian and Shobana[19] conducted a comparative study of IMPT, intensity modulated RT, helical tomotherapy, and volumetric-modulated arc therapy in 8 patients. They concluded that the doses to the lens, thyroid gland, lungs, heart, spleen, kidneys, esophagus, and optic nerve were significantly lower in the IMPT group.[19] In our study, the maximum dose to the lens exceeded 10 Gy (RBE), which created dose constraints in our hospital in 4 out of the 8 patients in the PSPT group because of the need to ensure a sufficient dose to the cribriform plate. In contrast, the maximum dose did not exceed the threshold in any of the

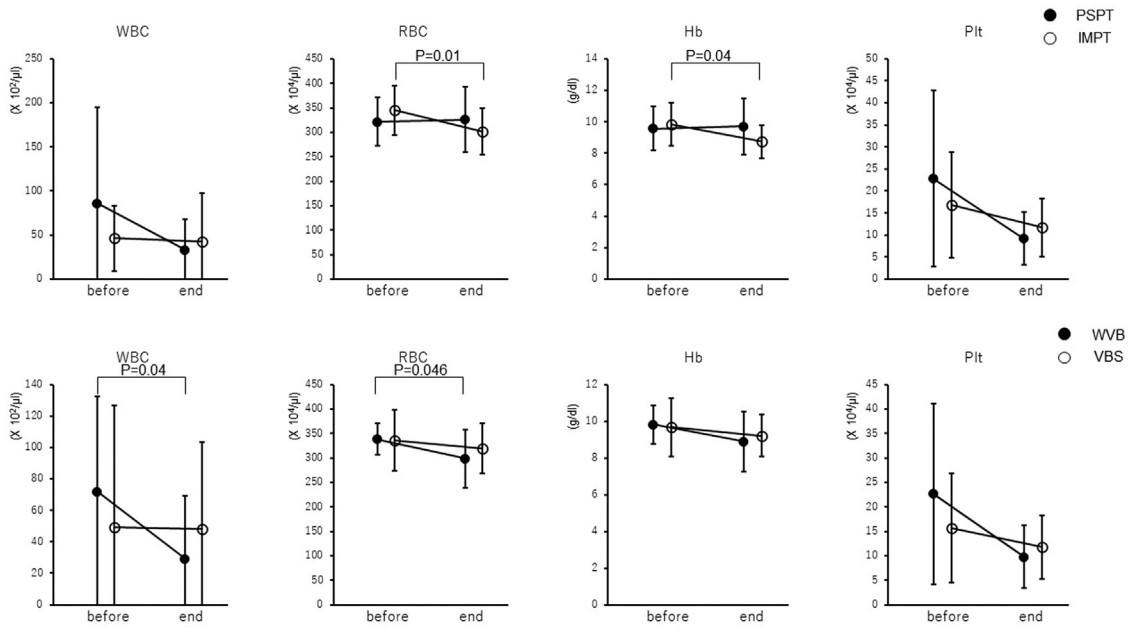

Figure 3 Change in blood cell counts. Upper: comparison of passive scattered proton beam therapy (PSPT) and intensity modulated proton beam therapy (IMPT); lower: comparison of whole vertebral body (WVB) and vertebral body sparing (VBS).

16 patients in the IMPT group. Although a significant dose reduction in IMPT was observed only in the lens, the irradiation dose to all the organs, including the esophagus, tended to be lower in the IMPT group than in the PSPT group, which is consistent with the results of past studies. Howell et al[21] classified the organs based on their location relative to the vertebral bodies (anterior type: esophagus, heart, thyroid gland; lateral type: kidneys and lungs; bilateral type: liver). They reported that anterior-type organs received a lower dose from PSPT than during photon RT because of the characteristics of the Bragg peak. In the present study, the OAR dose tended to be lower in the IMPT group than in the PSPT group for both anterior and lateral types, with similar trends. The Bragg peak is an effect specific to PBT, and we think that the effect is due to the difference in target dose sharpness, rather than the involvement of the Bragg peak. Our hypothesis is supported by the significantly lower INH for IMPT. Stoker et al[22] appreciated that IMPT can lower the lens dose, although the doses to the lungs and kidneys were higher—an effect that they attributed to the penumbra. They also proposed that appropriate aperture use would markedly diminish the penumbra. The major disadvantage of scanning beams is the larger lateral penumbra, compared with that for passive scattered beams.[23,24] Our system has a treatment nozzle that can deliver spot scanning beams and is equipped with a multileaf collimator (MLC). Thus, our facility's system was structured to be less affected by the penumbra than general scanning PBT facilities. Giantsoudi et al[18] proved that the VBS technique can achieve a decreased volumetric coverage of both the anterior and posterior vertebral bodies compared with the WVB technique in a simulation study examining 2 patients. Hashimoto et al[17] reported that the irradiated volume percentages of the heart, lungs, and abdominal cavity were quite small in all 9 patients who were treated using IMPT, and there was a significant reduction in the mean dose to the heart and abdominal cavity among the 5 patients who were treated using the VBS technique compared with that in the remaining 4 patients who were treated using the WVB technique. Our study revealed that the mean doses to the thyroid, lungs, esophagus, and kidneys in the VBS group were lower than those in the WVB group, similar to the results of past studies.

Howell et al[21] reported that the dose homogeneity of CTV was better in a PBT group than in a photon RT group. The present report is based on the results of PSPT. We reported that IMPT had a higher dose homogeneity than PSPT, which proves the sharpness of the target dose (ie, a superior dose fall-off). Giantsoudi et al[18] compared the dose around the CTV using several irradiation techniques and concluded that IMPT showed a better dose conformity than PSPT because of a superior sparing of the vertebral column. On the other hand, Stoker et al[22] reported that both PSPT and IMPT achieved clinically acceptable CTV coverage. Opinions and views regarding the target dose are not always consistent. However, to the best of our knowledge, there are no reports of inferior target coverage for IMPT. We do not think that there is a significant clinical difference between the target doses of PSPT and IMPT, but a minimum dose of 90.8% of the prescribed dose for PSPT seems somewhat unsatisfactory. In PSPT, the minimum PTV dose was less than 95% in all 8 patients. The reasons were a spread-out Bragg peak width limit in 7 patients, adjustments to the MLC and bolus parameters to comply with OAR dose constraints in 5 patients, and dose reduction at the field juncture in 5 patients. The area where we most struggled to adjust the MLC and bolus parameters because of the OAR dose constraints was the cribriform plate, which conflicted with the lens dose constraints. Dose reduction at the field junction occurred in cases where the junction had to be set at the cerebellar level in patients where the PTV sizes changed abruptly above and below the junction. We believe that IMPT can overcome these issues.

When it comes to hematologic toxicity, PBT is known to be safe with a minimal effect. Past studies have shown that hematologic toxicity was less prominent for PBT compared with photon RT during and for 4 weeks after CSI.[17] Yoo et al[25] reported that PBT resulted in a better recovery of the absolute lymphocyte and PLT counts than photon RT. We decided between using the WVB technique or the VBS technique based on the patient's age. As shown in the results, the WBC and RBC counts were significantly reduced and the hemoglobin and PLT counts tended to be reduced during the treatment period in the WVB group. The decreases in the mean values of all counts were more pronounced in the WVB group than in the VBS group, although these data are for reference only because the chemotherapy intensities were inconsistent. The WBC counts showed an unstable trend, but all the patients were receiving granulocyte colony-stimulating factor; the observed instability might have been caused by different medication timings. Overall, the degree of blood cell loss was not severe, and past studies have reported improvements after about 1 month. Thus, these results are considered clinically acceptable. Other than early hematologic toxicity, hair loss and hearing loss were common. Hair loss was seen mainly around the boost irradiation site. Hearing loss was thought to be caused by the anticancer drug cisplatin.

Recurrences were observed in 3 patients in the PSPT group and 1 patient in the IMPT group. Local recurrences were recognized in patients with choroid plexus tumor, medulloblastoma, and embryonal tumor. The remaining 1 patient with a germ cell tumor developed intracerebral dissemination. There were few cases of recurrence, and there was little commonality in the pattern of recurrence. With this in mind, the dose distribution and sites of recurrence were compared, and recurrence did not occur at sites with relatively low doses. Long-term follow-up of a larger number of patients may provide new findings.

We plan to continue providing follow-up care to these patients over a longer term.

Some limitation is included in this study. The sample size is by no means sufficient. So far, there are no findings suggesting adverse events due to overdose or recurrence due to insufficient dose. However, there is no way to increase the number of PSPT cases further, because the usual practice has been already shifted from PSPT to IMPT. We plan to accumulate IMPT cases and study its efficacy and safety in a greater number of patients.

Conclusion

IMPT can decrease the dose to the lens compared with PSPT. The VBS technique can decrease the doses to neck-chest-abdominal organs to a greater degree than the WVB technique. The PTV coverage of IMPT is superior to that of PSPT, with a minimum and homogeneous dose. Hematologic toxicity is mild.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101251.

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