Journal of Radiation Research, Vol. 62, No. 2, 2021, pp. 186–197
doi: 10.1093/jrr/rraa118
Advance Access Publication: 21 December 2020

Impact of lifetime attributable risk of radiation-induced secondary cancer in proton craniospinal irradiation with vertebral-body-sparing for young pediatric patients with medulloblastoma

Shunsuke Suzuki[1,*], Takahiro Kato[2,4] and Masao Murakami[3]

[1]Department of Radiation Oncology, Sapporo High functioning Radiation Therapy Center, Nishi-ku Miyanosawa 2-jo 1-chome 16-1, Sapporo City, Hokkaido 063-0052, Japan
[2]Department of Radiation Physics and Technology, Southern Tohoku Proton Therapy Center, Koriyama, Japan
[3]Department of Radiation Oncology, Southern Tohoku Proton Therapy Center, Koriyama, Japan
[4]Preparing Section for New Faculty of Medical Science, Fukushima Medical University, Fukushima, Japan
*Corresponding author. Hokkaido Ohno Memorial Hospital, 2-16-1 Miyanosawa, Nishi-ku, Sapporo City, Hokkaido, 063-0052, Japan. Tel: +81-011-665-0020; Email: Baseballtabletenis@me8.seikyou.ne.jp
(Received 7 May 2020; revised 31 August 2020; editorial decision 3 November 2020)

ABSTRACT

We used the method proposed by Schneider *et al. Theor Biol Med Model* 2011;8:27, to clarify how the radiation-induced secondary cancer incidence rate changes in patients after proton craniospinal irradiation (CSI) without and with vertebral-body-sparing (VBS). Eight patients aged 3–15 years who underwent proton CSI were enrolled in the study. For each case, two types of plan without and with VBS in the target were compared. The prescribed doses were assumed to be 23.4 Gy relative biological effectiveness (RBE) and 36 Gy (RBE). Using the dose–volume histograms of the two plans, the lifetime attributable risk (LAR) was calculated by both methods for each patient based on the dose data calculated using an XiO-M treatment planning system. Eight organs were analyzed as follows: lung, colon, stomach, small intestine, liver, bladder, thyroid and bone. When the prescribed dose used was 23.4 Gy (RBE), the average LAR differences and the average number needed to treat (NNT) between proton CSI without and with VBS were 4.04 and 24.8, respectively, whereas the average LAR difference and the average NNT were larger at 8.65 and 11.6, respectively, when the prescribed dose of 36 Gy (RBE) was used. The LAR for radiation-induced secondary cancer was significantly lower in proton CSI with VBS than without VBS in pediatric patients, especially for the colon, lung, stomach and thyroid. The results of this study could serve as reference data when considering how much of vertebral bodies should be included when performing proton CSI according to age in clinical settings.

Keywords: secondary cancer; proton therapy; lifetime attributable risk; craniospinal irradiation; vertebral-body-sparing; growth disorders

INTRODUCTION

The general term for malignant tumors from birth to the age of 20 is childhood cancer. In Japan, about 2500 people are diagnosed with childhood cancer annually [1]. Of these cases, medulloblastoma is the second most common childhood tumor in the central nervous system and is treated with surgery, chemotherapy and radiation therapy [2]. As radiation therapy, boost irradiation is generally performed on the tumor bed after craniospinal irradiation (CSI), and the prescribed dose is determined according to the grade. CSI needs to irradiate the whole brain and whole spinal canal with different beam arrangements, but it is necessary to maintain a uniform dose at the junction, which is considered to be one of the technically difficult irradiation techniques [3]. In general, whole spinal canal irradiation is performed in a single posterior direction, but when X-rays are used, there is a problem that normal tissues such as the heart, lungs, liver and intestinal tract cannot avoid exposure. Methods using intensity-modulated radiation therapy (IMRT), which can limit the high-dose area compared with conventional irradiation methods using a single posterior direction, are also being studied, but the spread of the low-dose area is inevitable, and future radiation-induced secondary cancer may not be avoidable [4]. Its impact has become a major concern and requires a careful and effective solution. As a means for overcoming this problem, the use of

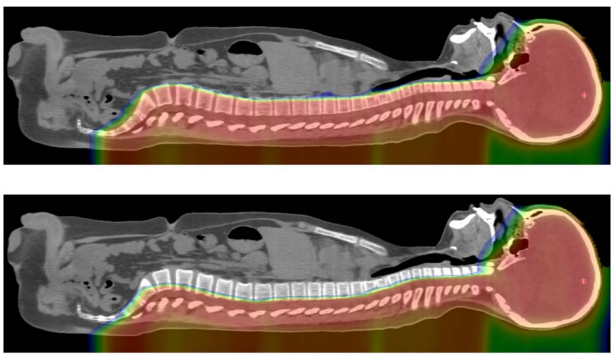

Fig. 1. Dose distributions at the midsagittal plane during proton CSI without VBS (top) and with VBS (bottom) on patient G.

a proton beam is conceivable, and its usefulness in clinical practice has recently been reported [5]. Since the proton beam has a finite range, it is possible to reduce the aforementioned exposure of normal tissue to zero by irradiating from the posterior direction. In Japan, proton therapy (PT) insurance has been applied to childhood cancer since April 2016, and the need for CSI using proton beams has increased.

Growth impairment measures are one of the important points in children that require different consideration compared with that in adults when performing radiation therapy during growth. There have been many reports of growth disorders in radiation therapy, and measures to address them have been studied [6]. For example, when a lesion is present in the vicinity of a vertebral body, and irradiation is performed such that the irradiation field partially includes the ipsilateral side of the vertebral body, growth of the irradiated portion is inhibited, and scoliosis may occur. For this reason, it is recommended that the entire vertebral body should be included in the radiation field [7]. Although it is inevitable that a growth disorder will occur due to this, it is thought that the occurrence of a functional disorder that can affect daily life due to scoliosis can be reduced. It has been pointed out that the risk of growth impairments may be dose-dependent [8], and it is controversial how far vertebral body needs to be included in the irradiation field. In CSI, it is common to include the entire vertebral body in growing patients, whereas MacEwan *et al.* performed irradiation without including vertebral bodies in six cases aged between 3 and 5 years. They reported long-term observations but reported no functional problems [9]. This result suggests that proton CSI in the anterior–posterior direction of the vertebral body may not necessarily require uniform dose coverage compared with proton CSI in the left–right direction. If it is not necessary to include the entire vertebral body in the irradiation field, proton beams can be used to limit the dose, making it possible to reduce acute radiation damage, bone marrow suppression and radiation-induced secondary cancer.

The most recent childhood cancer survivor study showed long-term survivors of childhood cancer who received radiation therapy have a significantly increased risk of developing second malignant neoplasms [10]. Because children survive for decades after overcoming cancer, they are more likely to develop late effects. It is difficult practically to observe the 5–70-year follow-up of radiation-induced secondary cancer. Using the data on the atomic bomb (A-bomb) survivors and carcinogenesis after radiation therapy, Schneider *et al.* [11] estimate the secondary cancer incidence in each organ. Lifetime attributable risk (LAR) can be calculated by the aforementioned method [11]. LAR of secondary cancer in CSI is reported to be lower with PT than that with IMRT [12–14], but the extent to which LAR changes without and with vertebral-body-sparing (VBS) in proton CSI is unknown as it has not been studied. By adopting VBS, there may be the merit of reducing radiation-induced secondary cancer and the disadvantage of increasing the probability of growth failure, but there is insufficient data that can be used as a basis for judgment, so it is not easy to make the appropriate judgment in a clinical setting. Currently, a clinical trial for proton CSI with VBS is ongoing [15], but it seems that it will take a considerable amount of time for results to become available. Therefore, in this study, we used the method proposed by Schneider *et al.* [11] to clarify how the radiation-induced secondary cancer incidence rate changes in patients after proton CSI without and with VBS.

MATERIALS AND METHODS

Proton CSI method

A total of eight patients aged 3–15 years who underwent proton CSI were enrolled in this study as subjects. The study was approved by the institutional review board of our institution. Table 1 shows the patient data. The irradiation positions were all supine, the head was fixed by a thermoplastic shell, and the body trunk was fixed by a vacuum cushion. Computed tomography (CT) images of the whole body with a slice thickness of 2 mm were obtained by using Aquilion LB (Canon Medical Systems, Otawara, Japan). Hitachi's proton-type Particle Therapy System (Hitachi, Ltd., Kashiwa, Japan) was used in this study. This machine employs a wobbler method, which is one of the passive scattering (PS) methods [16]. The cranial fields were considered out of the three directions, with two posterior oblique directions and one posterior direction to protect the lens. The spinal field consisted of one posterior direction, but the irradiation field did not sufficiently cover the entire spinal canal, so the multiple irradiation fields were matched. The number of irradiation fields for matching differed from case to case depending on spine length but matching was usually performed on 3–4 irradiation fields. The moving junction method with three joints was adopted as a measure against joint uncertainty. The irradiation field was formed by multileaf collimator (MLC), and the joints were changed on a daily basis. A commercially available treatment planning system (TPS) XiO-M (Elekta, Stockholm, Sweden) was used to calculate the dose distributions in proton CSI.

For each case, two types of plan (a total of 16 plans) without and with VBS in proton CSI were performed. According to the report of Hoeben *et al.* [17], the clinical target volume (CTV) is defined as the whole cerebrospinal cavity when no vertebral body is included, and adding vertebral body to it only when the vertebral body is included. The distal and proximal margins and smearing margins were fundamentally calculated by using Strategy 2 as reported by Moyers *et al.* [18]. The radiation field was formed using the MLC built in the snout, and the lateral margin was set to 10 mm. Fig. 1 shows an example of typical dose distributions in proton CSI without and with VBS. In both plans, the cranial fields are exactly the same, and only the dose distributions in and around the vertebral body are different. According to grade, the prescribed doses used were 23.4 Gy relative biological effectiveness (RBE)/13 fractions (Fr) and 36

Table 1. Patient information

	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G	Patient H
Age (years)	3	5	5	8	10	10	12	15
Sex	F	F	M	M	F	M	M	M
Length from parietal to coccyx (cm)	49.5	57.9	58.3	63.1	63.6	70.2	76.2	77.9

Table 2. Schneider's fit parameters for each dose–response model for carcinoma induction

Organ at risk	Linear model	Full model		Mono-modal model	Plateau model	β_{JP}[b]	γ_e	γ_α
	β[b]	α[a]	R	α[a]	α[a]			
Lung		0.042	0.83	0.022	0.056	7.5	0.002	4.23
Colon	7.2	0.001	0.99	0.001	0.001	8	−0.056	6.9
Stomach		0.46	0.46	0.111		9.5	−0.002	1.9
Small intestine		0.591	0.09	0.48		8	−0.056	6.9
Liver	0.22	0.323	0.29	0.243	0.798	4.3	−0.021	3.6
Bladder		0.219	0.06	0.213	0.633	3.2	−0.024	2.38
Thyroid				0.033		0.13	−0.046	0.6

Table 3. Schneider's fit parameters for each dose–response model for sarcoma induction

Organ at risk	Low repopulation			Intermediate repopulation			Full tissue recovery			γ_e	γ_α
	α[a]	R	β[b]	α[a]	R	β[b]	α[a]	R	β[b]		
Bone	0.019	0.1	1.7	0.067	0.5	0.2	0.078	1	0.1	−0.013	−0.56

Gy (RBE)/20 Fr. The former is applied to the standard-risk group and the latter to the high-risk group dose prescription.

LAR calculation

Schneider *et al.* used the data on A-bomb survivors and carcinogenesis after radiation therapy to propose a method using LAR as the radiation-induced secondary cancer incidence rate for each organ [11]. The equations used in this study, based on the method proposed by Schneider *et al.* [11], are shown in equations (1–5). Eight organs were analyzed as follows: lung, colon, stomach, small intestine, liver, bladder, thyroid and bone. Their parameters are shown in Tables 2 and 3 and Fig. 2. The brain and soft tissues were excluded from the analysis because the whole brain irradiation was performed under the same conditions in both methods, and the exposed volume of the soft tissues on the proximal side of the CTV in whole spinal canal irradiation was considered to be almost the same.

The risk equivalent dose (RED) has three dose response–models, linear, mono-modal and plateau, which are applied to determine the relationship between the dose and risk of radiation-induced secondary cancer. We call the bell-shaped model the mono-modal model. That is because in general, the bell shape means symmetrical distribution like the normal distribution. The bell shaped-model described by Schneider *et al.* [11] is the skewed normal distribution. The various organs have been reported to be best fitted by one or the other of these models [19–23]. The linear, mono-modal and plateau models are shown in equations (1–3), respectively:

$$\mathrm{RED}(D) = D \tag{1}$$

$$\mathrm{RED}(D) = D\mathrm{e}^{-\alpha' D} \tag{2}$$

$$\mathrm{RED}(D) = \frac{\mathrm{e}^{-\alpha' D}}{\alpha'} \tag{3}$$

Schneider *et al.* have proposed a full model that integrates all three models into one formula [24]. The RED calculation formula for cancer induction is as follows:

$$\mathrm{RED}(D) = \frac{\mathrm{e}^{\alpha' D}}{\alpha' R}\left(1 - 2R + R^2\mathrm{e}^{\alpha' D} - (1-R)^2\mathrm{e}^{-\frac{\alpha' R}{1-R}D}\right) \tag{4}$$

$$\alpha' = \alpha + \beta\frac{\mathrm{d_f}}{\mathrm{D_T}}\mathrm{D}$$

D is the dose, R and α' are organ-specific model parameters (R is a repopulation/repair parameter and α' is a cell killing parameter), D_T is the prescribed dose and d_f is the fraction dose, e is defined as the base of the natural logarithm.

Next, the RED calculation formula for sarcoma induction is as follows:

$$\mathrm{RED}(D) = \frac{\mathrm{e}^{-\alpha' D}}{\alpha' R}\left(1 - 2R + R^2\mathrm{e}^{\alpha' D} - (1-R)^2\mathrm{e}^{-\frac{\alpha' R}{1-R}D} - a' RD\right) \tag{5}$$

Using CT and TPS, the dose D_i at the i-th point in the organ at risk (OAR), is calculated. OAR dose–volume histograms (DVH) derived

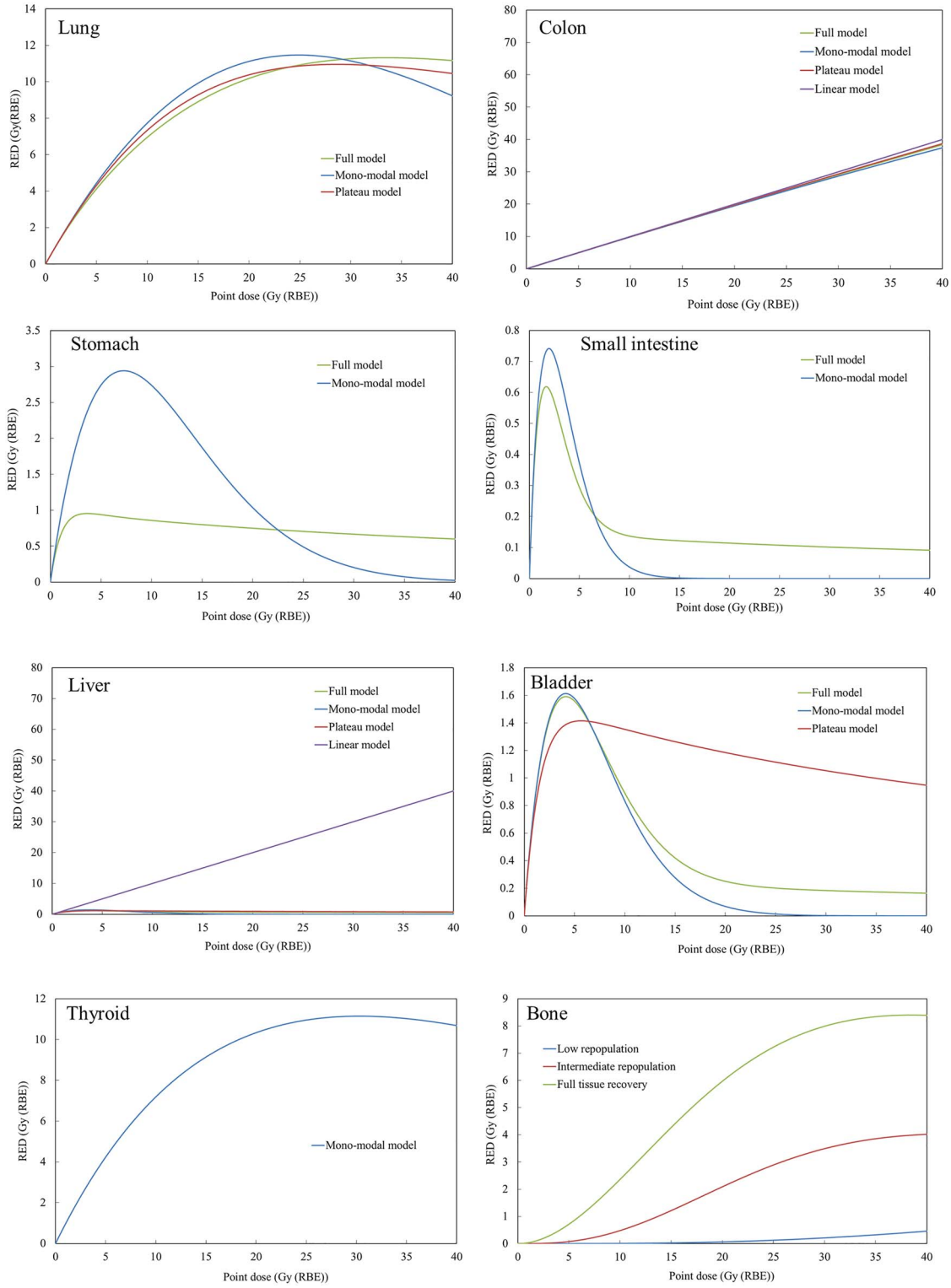

Fig. 2. RED for eight organs at risk based on parameters in Tables 2 and 3.

using CT data are patient-specific and treatment-specific. Thus, using DVH, the total risk of secondary cancer in the OAR in a patient can be calculated by the following formula (equation 6). As the overall risk of secondary cancer in the OAR, the organ equivalent dose (OED) is calculated using DVH and RED as follows:

$$OED = \frac{1}{V_T}\sum_i V(D_i)\, RED(D_i) \tag{6}$$

Here, V_T is the total organ volume, and $V(D_i)$ is the i-th dose volume of the OAR that is irradiated to dose D_i. Using the age at exposure to radiation therapy and the attained age, the excess absolute risk (EAR) at the attained age can be determined by the following formula (the parameters for this equation are based on the previously published cancer risk data from A-bomb survivors [25, 26] and patients receiving radiation for Hodgkin's lymphoma [20, 22, 27]):

$$EAR(D, e, a, s) = OED \bullet \beta \bullet \exp\left(\gamma_e (e-30) + \gamma_a \ln\left(\frac{a}{70}\right)\right) \bullet (1 \pm s) \tag{7}$$

Here, β is the initial gradient of the gender-averaged EAR at 1 Gy of the A-bomb survivors, γ_e and γ_a are the risk modification parameters for age at exposure (**e**) and attained age (**a**), respectively, and s is the risk modification factor for gender: 0.15 for females and − 0.17 for males [26].

To calculate a patient's LAR of secondary cancer, the following formula can be used:

$$LAR(D, e, a) = \int_{a=e+L}^{a_{max}} EAR(D, e, a, s) \bullet \frac{s(a)}{s(e)} da \tag{8}$$

Here, $s(a)/s(e)$ is the probability of survival from age e to age a, and L is the minimum latency of solid tumor induction (5 years for solid cancer and 2 years for leukemia) [28].

The parameters used in the calculations were derived from the work of Schneider *et al.* [11]. However, since there are no data on the thyroid in this paper, the data from another paper by Schneider using a bell-shaped model were used [22]. In the previous paper, the β values for the EAR calculation were derived from the data transformed to be applicable to British patients [29]. However, since all patients were Japanese in this study, we used the original data from the A-bomb survivors in Japan. The essential area of LAR ranges from the attained age to 5–75 years. In addition, the values of $s(a)$ and $s(e)$ were taken from the 2011 life table of Japan, not from the US data in Schneider's paper.

If multiple dose–response curves were obtained, the LAR of the dose–response curve was calculated as the LAR for this patient along with the LAR loading average.

In addition to the LAR differences between proton CSI without VBS and proton CSI with VBS in each organ, the number needed to treat (NNT) was also calculated. NNT represents the reciprocal of LAR divided by 100 and means the number of patients required for treatment. NNT is the number that indicates how many people need to be treated before one person can benefit from a given intervention.

Statistical analysis

The statistical analysis was performed using the mean value of the LAR in proton CSI without and with VBS. Since Schneider's parameter is 10 000 person years, the value that comes out is the number of occurrences per 10 000 people. Therefore, it is necessary to calculate the number of occurrences per individual by dividing by 10 000 and multiplying by 100 to show the value as a percentage. For each of the eight organs of eight patients, a t-test of the difference in means of the two corresponding groups (without and with VBS) was performed; an upper one-tailed t-test was used to determine the statistical significance of the effects of the two treatments. All statistical analyses were performed using the statistical discovery software JMP Pro version 12 (SAS Institute Inc., Cary, NC, USA). In addition, we investigated the causal relationship of prescription dose, age and gender for each organ, and the validity of LAR difference results. The hybrid log–normal (HLN) model described by Kumazawa *et al.* [30] was used to confirm the validity of LAR differences.

RESULTS

Fig. 3 shows the mean DVH among eight patients by each organ when the prescribed dose used was 36 Gy (RBE)/20 Fr. It shows that the exposure in all analyzed organs is greatly reduced in proton CSI with VBS. This tendency was the same even when the prescribed dose used was 23.4 Gy (RBE)/13 Fr. Tables 4 and 5 show the LAR of each organ without and with VBS at 23.4 Gy (RBE)/13 Fr, respectively. Table 6 shows the LAR differences when the prescribed dose used was 23.4 Gy (RBE)/13 Fr. In the same way, Tables 7 and 8 show the LAR of each organ without and with VBS at 36 Gy (RBE)/20 Fr, respectively. Table 9 shows the LAR differences when the prescribed dose used was 36 Gy (RBE)/20 Fr. At any given dose, LAR differences were positive in all analyzed organs. Significant differences were observed in seven organs, except for the bladder, with 23.4 Gy (RBE)/13 Fr prescribed dose and in eight organs with the 36 Gy (RBE)/20 Fr prescribed dose. The organ with the largest LAR differences was the colon, followed by the lung, and then the stomach or thyroid depending on the prescribed dose. The integrated values of the LAR difference average and the average value of NNT between proton CSI without and with VBS were 4.04% and 24.8, respectively, for 23.4 Gy (RBE)/13 Fr prescribed dose; whereas, the average LAR difference value was large at 8.65% and the average NNT value was 11.6 for 36 Gy (RBE)/20 Fr prescribed dose. Fig. 4 shows the ratio of LAR differences for each prescribed dose for each organ. It can be seen that the 36 Gy (RBE)/23.4 Gy (RBE) ratio of LAR differences increases with age, except for the bladder which has a low exposure dose. Fig. 5 shows the gender ratio male/female (M/F) of LAR difference by age. This is the result of examining patients B and C at 5 years old and patient E and F at 10 years old. The results show that males tended to have higher LAR differences at 5 years old, especially in the thyroid and colon than at 10 years old. Fig. 6 shows the results of the HLN model of LAR differences pooling all data in Tables 6 and 9. It can be seen that most plots of the two datasets were included within the 95% prediction interval (PI).

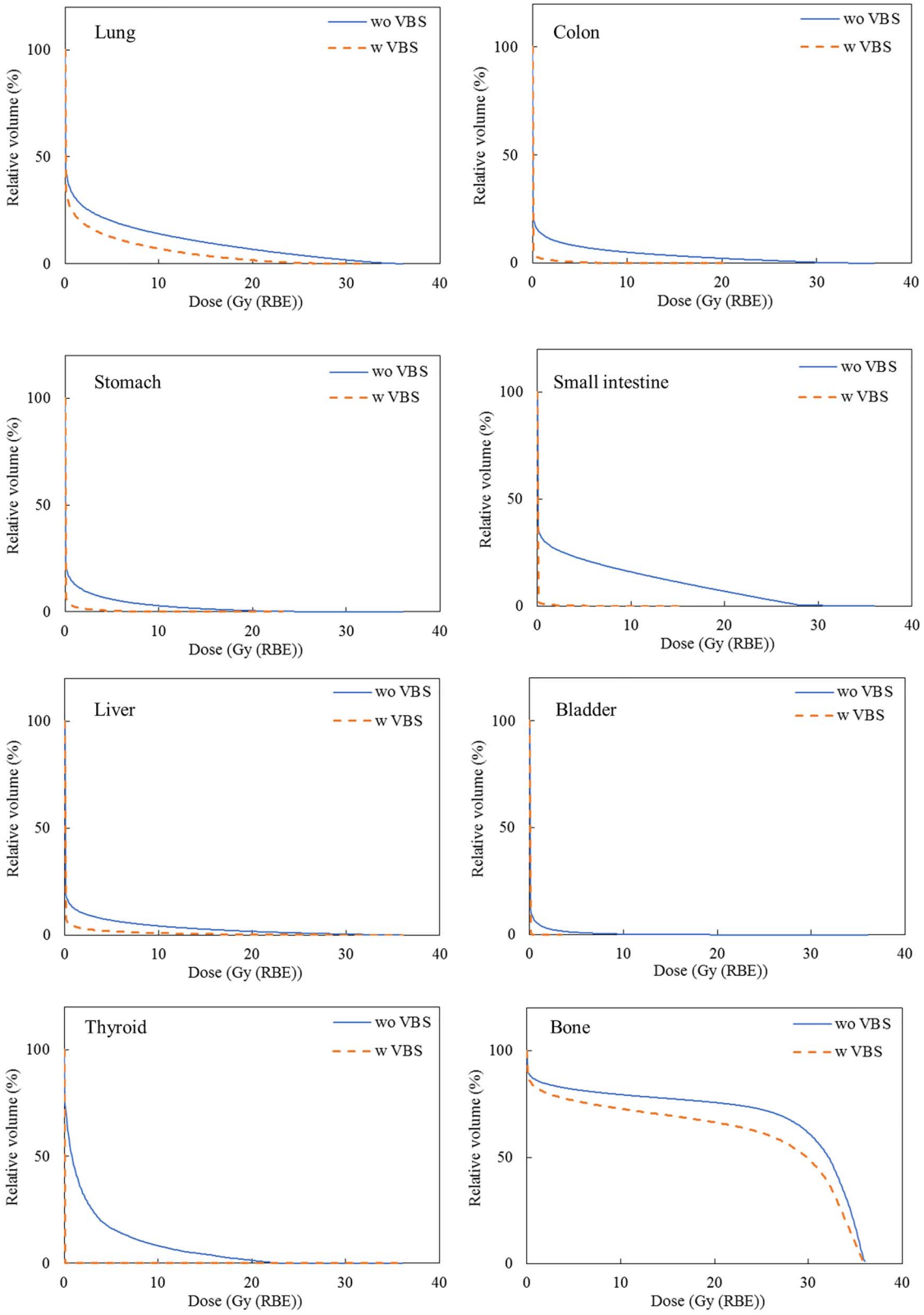

Fig. 3. Population mean dose–volume histograms ($n = 8$) from two planning techniques shown for each analyzed organ when the prescribed dose of 36 Gy (RBE)/20 Fr is used. Orange dotted lines and blue solid lines indicate proton craniospinal irradiation with and without VBS, respectively. wo VBS = without VBS, w VBS = with vertebral-body-sparing.

Table 4. LAR of proton CSI without VBS for each OAR when the prescribed dose of 23.4 Gy (RBE)/13 Fr is used

Organ at risk	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G	Patient H	Average
Lung	271.4	192.1	118.2	151.0	136.0	257.5	146.4	34.3	163.4
Colon	601.5	32.8	477.7	161.7	337.1	221.8	157.5	9.4	249.9
Stomach	55.2	73.2	22.3	29.8	37.2	50.8	36.1	1.0	38.2
Small intestine	33.8	42.4	38.4	39.1	7.3	21.6	11.1	1.5	24.4
Liver	15.2	9.0	8.8	11.8	9.4	9.7	6.7	0.9	8.9
Bladder	8.3	1.5	0.0	19.8	0.0	4.9	0.0	1.1	4.5
Thyroid	73.1	0.3	77.1	22.6	25.1	3.8	2.3	0.8	25.6
Bone	54.3	49.5	37.3	29.0	39.9	30.0	25.9	22.1	36.0
Cumulative	1534.0	893.9	1106.2	764.0	1037.7	882.6	659.2	324.2	900.2

Table 5. LAR of proton CSI with VBS for each OAR when the prescribed dose of 23.4 Gy (RBE)/13 Fr is used

Organ at risk	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G	Patient H	Average
Lung	167.46	127.02	89.64	85.54	64.16	86.98	95.20	7.53	90.44
Colon	52.67	1.48	16.40	3.59	12.75	3.96	23.20	0.00	14.26
Stomach	0.92	19.82	10.14	2.26	1.09	1.55	16.90	0.00	6.58
Small intestine	3.08	3.49	6.83	6.10	0.00	0.00	1.10	0.00	2.57
Liver	4.81	3.71	3.08	3.07	2.97	3.03	2.70	0.04	2.93
Bladder	0.02	0.00	0.00	0.43	0.00	0.00	0.00	0.00	0.06
Thyroid	0.00	0.00	0.43	0.00	0.00	0.00	0.00	0.00	0.05
Bone	48.71	42.61	32.93	23.69	32.88	23.19	20.40	16.85	30.16
Cumulative	797.54	687.03	485.84	423.99	551.12	401.25	432.70	277.54	507.13

Table 6. LAR differences (%) between proton CSI without and with VBS and the NNT values for each OAR when the prescribed dose of 23.4 Gy (RBE)/13 Fr is used

Organ at risk	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G	Patient H	Average	SD	NNT	*P* value
Lung	1.04	0.65	0.29	0.65	0.72	1.71	0.51	0.27	0.73	0.44	137.1	0.002
Colon	5.49	0.31	4.61	1.58	3.24	2.18	1.34	0.09	2.36	1.82	42.4	0.006
Stomach	0.54	0.53	0.12	0.28	0.36	0.49	0.19	0.01	0.32	0.19	316.1	0.001
Small intestine	0.31	0.39	0.32	0.33	0.07	0.22	0.10	0.02	0.22	0.13	458.1	0.001
Liver	0.10	0.05	0.06	0.09	0.06	0.07	0.04	0.01	0.06	0.03	1666.1	<0.001
Bladder	0.08	0.02	0.00	0.19	0.00	0.05	0.00	0.01	0.04	0.06	2273.4	0.05
Thyroid	0.73	0.00	0.77	0.23	0.25	0.04	0.02	0.01	0.26	0.30	390.9	0.03
Bone	0.06	0.07	0.04	0.05	0.07	0.07	0.06	0.05	0.06	0.01	1708.5	<0.001
Cumulative	8.35	2.03	6.20	3.40	4.78	4.81	2.27	0.47	4.04	2.37	24.8	0.001

DISCUSSION

In childhood cancer, when the target tumor is located in the vicinity of a vertebral body during radiation therapy, it has been conventionally practiced to uniformly irradiate the target tumor including the vertebral body in order to suppress growth disorders [7]. In recent years, the usefulness of proton CSI has been reported [5]. In proton CSI for young pediatric patients, it is also common to include the entire vertebral body in the irradiation field. In contrast, MacEwan *et al.* reported long-term follow-up in proton CSI with VBS [9], which showed impaired growth of the posterior margin of the vertebral body, but there was complementary expansion of the intervertebral disc, and no functional impairment. This suggests that VBS may be acceptable in the anteroposterior direction compared with the lateral direction. If VBS can be adopted, it can be expected that the incidence of acute disorders, such as esophagitis and myelosuppression, and radiation-induced secondary cancer can be reduced. While the reduction in incidence of acute disorders such as esophagitis and myelosuppression can be predicted to some extent from the results of dose distribution and DVH, the extent to which VBS can reduce the incidence rate of radiation-induced secondary cancer, which is of great concern in pediatric cancer treatment, is unclear. Therefore, we calculated and compared the radiation-induced secondary cancer incidence rates in patients after proton CSI without and with VBS using the method proposed by Schneider *et al.* [11]. The results show that the organs

Table 7. LAR of proton CSI without VBS for each OAR when the prescribed dose of 36 Gy (RBE)/20 Fr is used

Organ at risk	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G	Patient H	Average
Lung	378.96	303.28	279.64	350.85	220.57	546.92	349.64	95.21	315.63
Colon	1006.29	73.73	1490.22	506.35	697.70	718.77	524.42	32.70	631.27
Stomach	87.84	101.84	48.80	71.24	60.49	107.93	80.68	3.00	70.23
Small intestine	72.75	56.40	40.06	71.11	13.23	42.43	24.18	3.76	40.49
Liver	23.29	14.18	20.21	26.62	13.22	22.00	16.00	2.28	17.23
Bladder	20.32	2.06	0.00	29.44	0.06	9.22	0.00	2.12	7.90
Thyroid	98.54	1.01	116.78	45.36	34.37	16.06	5.96	2.69	40.10
Bone	86.17	80.96	83.64	67.49	63.94	67.78	61.13	53.16	70.53
Cumulative	1774.15	633.46	2079.35	1168.47	1103.59	1531.11	1062.01	194.94	1193.39

Table 8. LAR of proton CSI with VBS for each OAR when the prescribed dose of 36 Gy (RBE)/20 Fr is used

Organ at risk	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G	Patient H	Average
Lung	275.08	215.85	231.72	219.80	118.78	220.38	246.17	23.66	193.93
Colon	116.55	4.14	56.15	13.19	38.33	13.91	82.66	0.00	40.62
Stomach	2.03	34.70	25.10	7.08	2.46	4.82	44.32	0.00	15.06
Small intestine	3.61	5.57	4.82	14.48	0.00	0.00	2.85	0.00	3.92
Liver	7.98	6.20	7.70	7.70	4.55	7.60	6.84	0.12	6.09
Bladder	0.15	0.00	0.00	1.56	0.00	0.00	0.00	0.00	0.21
Thyroid	0.00	0.00	59.14	0.00	0.00	0.00	0.00	0.00	7.39
Bone	78.74	71.56	77.23	57.88	54.72	56.34	50.24	41.91	61.08
Cumulative	484.14	338.01	461.85	321.70	218.84	303.04	433.08	65.70	328.30

Table 9. LAR differences (%) between proton CSI without and with VBS and the NNT values for each OAR when the prescribed dose of 36 Gy (RBE)/20 Fr is used

Organ at risk	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G	Patient H	Average	SD	NNT	*P* value
Lung	1.04	0.87	0.48	1.31	1.02	3.27	1.03	0.72	1.22	0.81	82.2	0.003
Colon	8.90	0.70	14.34	4.93	6.59	7.05	4.42	0.33	5.91	4.23	16.9	0.04
Stomach	0.86	0.67	0.24	0.64	0.58	1.03	0.36	0.03	0.55	0.31	181.3	0.01
Small intestine	0.69	0.51	0.35	0.57	0.13	0.42	0.21	0.04	0.37	0.21	273.4	0.01
Liver	0.15	0.08	0.13	0.19	0.09	0.14	0.09	0.02	0.11	0.05	897.7	<0.001
Bladder	0.20	0.02	0.00	0.28	0.00	0.09	0.00	0.02	0.08	0.10	1300.4	0.04
Thyroid	0.99	0.01	0.58	0.45	0.34	0.16	0.06	0.03	0.33	0.32	305.8	0.01
Bone	0.07	0.09	0.06	0.10	0.09	0.11	0.11	0.11	0.09	0.02	1057.4	<0.001
Cumulative	12.90	2.95	16.17	8.47	8.85	12.28	6.29	1.29	8.65	4.74	11.6	<0.001

with relatively large LAR differences were the colon, lung, stomach and thyroid. It was confirmed that VBS significantly reduced the LAR in all organs except bladder at 23.4 Gy (RBE)/13 Fr and in all organs at 36 Gy (RBE)/20 Fr. Specifically, the integrated value of NNT was 11.6 when the prescribed dose used was 36 Gy (RBE)/20 Fr, and a remarkable difference was found in the colon with CSI of 23.4 Gy (RBE)/13 Fr where the NNT value was 42.4. The LAR showed slightly different tendencies in some organs.

From Fig. 4, it can be said that the ratio of the LAR difference depending on the presence or absence of VBS increases with increasing age. It is considered that the ratio increases as the age increases because the size of the vertebral body increases with growth, and the peripheral organs dose in proton CSI with VBS increases significantly compared with proton CSI without VBS. In addition, since the ratios are all >1, it can be seen that the LAR difference due to the presence or absence of VBS is more remarkable in 36 Gy (RBE) than in 23.4 Gy (RBE). Therefore, in the case of 36 Gy (RBE), it is considered that the secondary carcinogenesis rate can be further lowered by better considering VBS and making a treatment plan than in the case of 23.4 Gy (RBE).

Although the mechanism of injuries when performing radiation therapy on vertebral bodies has not been fully elucidated, it has long been known that these injuries are dose-dependent [8]. In this study, the evaluation was performed under the same treatment plan assuming two patterns of prescribed doses, but the LAR showed slightly different

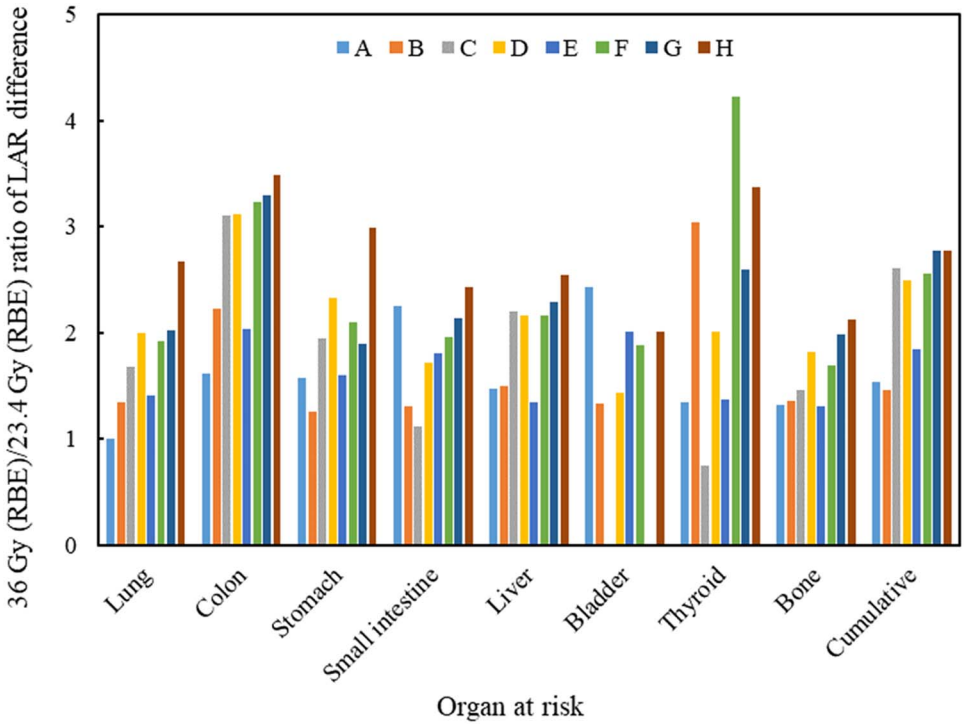

Fig. 4. The ratio data of LAR difference (age, organ) for each prescribed dose: Table 9 (36 Gy (RBE))/Table 4 (23.4 Gy (RBE)).

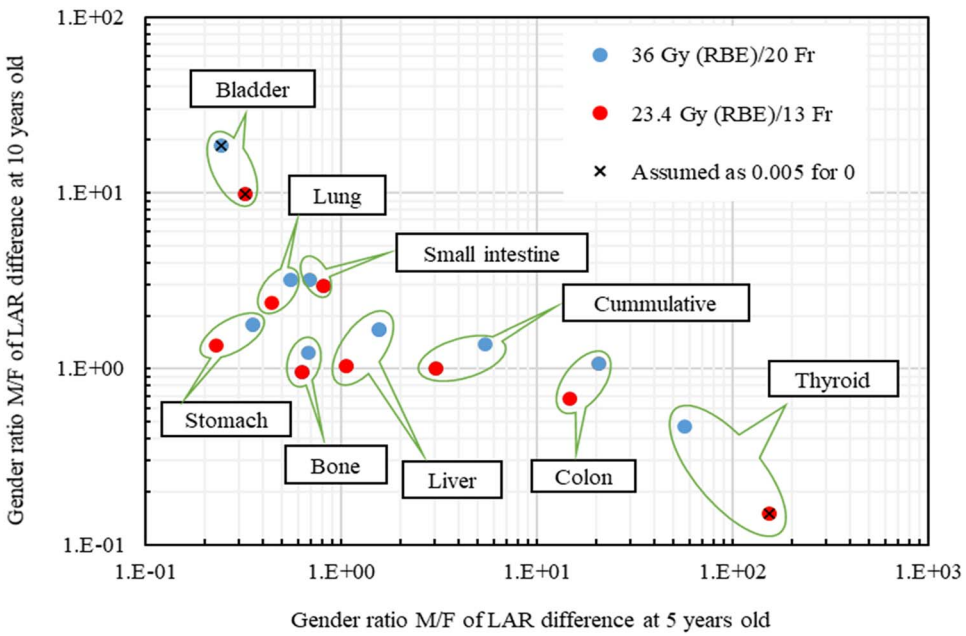

Fig. 5. Gender ratio M/F of LAR difference by age.

tendencies in some organs. By reviewing previous reports, Hoeben *et al.* provided an index for dose gradients in the vertebral body and a flowchart stratified by age [17]. At present, there is not enough evidence to actively adopt VBS as reported by MacEwan *et al.* [9], so based on the flowchart shown by Hoeben *et al.*, the vertebral body dose coverage should be adjusted according to age and prescribed dose. In this study, LAR was evaluated assuming that the vertebral body was completely covered or not, so if a treatment plan was created based

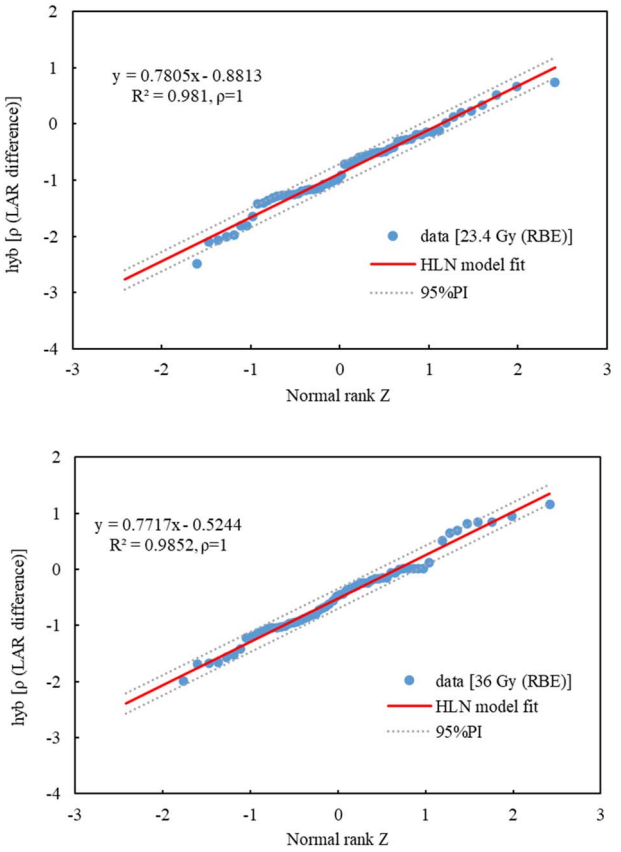

Fig. 6. HLN model of LAR differences pooling all data in Tables 6 (23.4 Gy (RBE)) and 9 (36 Gy (RBE)).

on the flowchart, the effect on LAR would be smaller than the results shown in this study. Therefore, the results of this study should be referred to only after understanding the prerequisites.

In this study, analysis was performed on eight cases. The colon results vary widely from case to case, and are remarkable even when comparing cases B and C of the same age. This was presumed to be due to the fact that the intestinal tract was located near the irradiation field at the time of CT imaging, or that there were individual differences in shape and size of the intestinal tract. There are various opinions about the effects of gender on growth disorders, but it is pointed out that females at the ages of 12–15 years are less affected by growth disorders because females grow faster [17]. Therefore, it may be acceptable to consider VBS actively in such cases. Comparing radiation-induced secondary cancer incidence rates in males and females of the same age, when the prescribed dose used was 36 Gy (RBE)/20 Fr, at the age of 5 years, the sum of LAR differences was 16.17 in males and 2.95 in females, which indicates that LAR differences are larger in males than in females. At the age of 10 years, LAR differences were 12.28 in males and 8.85 in females. In this case, the LAR differences in males were slightly larger than in females. From Fig. 5, it can be confirmed that the M/F gender ratio of LAR differences for the thyroid and colon is higher in the 5- than in the 10-year olds. Therefore, especially in the thyroid and colon, it is suggested that the influence of VBS on LAR difference may be greater in males as they are younger. However, the results are based on two sets of limited data and cannot be said to be a universal conclusion. Gender difference may be more pronounced and have a larger impact on incidence rates of radiation-induced secondary cancer in younger populations, and we intend to continue studying this by increasing the number of cases analyzed in the future.

Figure 6 was constructed to examine the homogeneity in normality derived by transforming the data of eight patients with eight OARs shown in Tables 6 and 9. These data are best approximated by the HLN model described by Kumazawa *et al.* [30]. As can be seen from Fig. 6, most plots of the two datasets were included within the 95% PI of Tables 6 and 9, respectively. Therefore, the data obtained in this study are considered to be reliable.

Several studies have reported on the radiation-induced secondary cancer incidence rate in proton CSI [12–14]. All of these reports conclude that the PT can significantly reduce LAR compared to IMRT, but no report mentions the effect of target range. There have been reports of the occurrence of secondary bone sarcoma after childhood cancer treatment, and it is known to occur even at <45 Gy (RBE) [31]. Due to the low prescribing dose in CSI, the average NNT values between proton CSI without and with VBS, when the prescribed doses used were 23.4 Gy (RBE)/13 Fr and 36 Gy (RBE)/20 Fr, were 24.8/10 000 person years and 11.6/10 000 person years, respectively. It is clearly important to consider the dose applied to the vertebral body, as reported by Koshy *et al.* [32].

In this study, PS is adopted as the proton beam irradiation method, but in recent years, pencil beam scanning (PBS) methods have been widely used. The use of PBS has significant technical advantages, such as the ability to reduce the uncertainty of the dose distribution by setting the Dose gradients [33], but the dose distribution itself obtained in the treatment plan is almost the same. Therefore it is thought that the results obtained in the present study can also be applied to proton CSI with PBS, which will become more popular in the future. On the other hand, it is known that the neutron exposure is larger in PS than in PBS [34], but since the neutron exposure cannot be considered on the TPS, the LAR evaluation cannot include the effects of neutrons in any case. This is a limitation of this study. Even if PS is used, the irradiation field-forming method differs for each apparatus, and the neutron contamination rate changes accordingly. Although it is much less in PBS than in PS, neutron contamination also occurs in PBS to some extent, and evaluation of LAR including neutron exposure is considered to be work for the future [35].

Another limitation of this study is that we did not fully validate the model used for LAR calculations. Careful follow-up of patients after proton CSI should be performed to confirm if the differences predicted in this study are observed. Currently, a clinical trial is ongoing analyzing the effect of proton CSI with VBS at Massachusetts General Hospital [15]. The clinical trial looks at early bone marrow changes in the vertebral body, spinal column changes, and the time until spinal curvature abnormalities occur. It is expected that future results will attract attention, and its relevance to this study will be a subject for future study.

CONCLUSION

In this study, we evaluated how the radiation-induced secondary cancer incidence rate changes in patients following proton CSI without

and with the VBS in proton CSI by using the method proposed by Schneider *et al.* [11] in childhood cancer. The LAR for radiation-induced secondary cancer was significantly lower in pediatric patients following proton CSI with VBS than after proton CSI without VBS, especially for the colon, lung, stomach and thyroid.

Although there is currently insufficient evidence to actively recommend VBS, we believe that the results of this study could serve as reference data when considering how much vertebral bodies should be included during irradiation according to age in clinical settings. In addition, prior informed consent of the family is important in performing proton CSI, and the results of this study are expected to be useful as reference data for explaining the risks and benefits of this treatment.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Miyoshi Y, Yorifuji T, Horikawa R et al. Childbirth and fertility preservation in childhood and adolescent cancer patients: A second national survey of Japanese pediatric endocrinologists. *Clin Pediatr Endocrinol* 2017; 26(2), 81–88.
2. Rickert CH, Paulus W. Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. *Childs Nerv. Syst.* 2011;17(9): 503–11.
3. Yamashita H, Kase Y, Murayama S. Simplified estimation method for dose distributions around field junctions in proton craniospinal irradiation. *Radiol. Phys. Technol.* 2017;10(1): 95–105.
4. Bernier V, Klein O. Late effects of craniospinal irradiation for medulloblastomas in paediatric patients. *Neurochirurgie*. 2018;S0028-3770(18)30034–1.
5. Sethi RV, Shih HA, Yeap BY et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. *Cancer* 2014;120(1): 126–33.
6. Hartley KA, Li C, Laningham FH et al. Vertebral body growth after craniospinal irradiation. *Int. J. Radiat. Oncol. Biol. Phys.* 2008;70(5): 1343–9.
7. Giebeler A, Newhauser WD, Amos RA et al. Standardized treatment planning methodology for passively scattered proton craniospinal irradiation. *Radiat. Oncol.* 2013;8:32.
8. Dörr W, Kallfels S, Herrmann T. Late bone and soft tissue sequelae of childhood radiotherapy. Relevance of treatment age and radiation dose in 146 children treated between 1970 and 1997. *Strahlenther. Onkol.*. 2013;189(7): 529–34.
9. MacEwan I, Chou B, Moretz J et al. Effects of vertebral-body-sparing proton craniospinal irradiation on the spine of young pediatric patients with medulloblastoma. *Adv. Radiat. Oncol.* 2017;2(2):220–227.
10. Friedman DL, Whitton J, Leisenring W et al. Subsequent neoplasms in 5-year survivors of childhood cancer: The childhood cancer survivor study. *J. Natl. Cancer Inst.* 2010;102(14): 1083–95.
11. Schneider U, Sumila M, Robotka J. Site-specific dose-response relationships for cancer induction from the combined Japanese A-bomb and Hodgkin cohorts for doses relevant to radiotherapy. *Schneider et al. Theoretical Biology and Medical Modelling* 2011;8:27.
12. Stokkevåg CH, Engeseth GM, Ytre-Hauge KS et al. Estimated risk of radiation-induced cancer following paediatric cranio-spinal irradiation with electron, photon and proton therapy. *Acta Oncol.* 2014;53(8): 1048–57.
13. Tamura M, Sakurai H, Mizumoto M et al. Lifetime attributable risk of radiation-induced secondary cancer from proton beam therapy compared with that of intensity-modulated X-ray therapy in randomly sampled pediatric cancer patients. *J. Radiat. Res.* 2017;58(3): 363–371.
14. Sakthivel V, Ganesh KM, McKenzie C et al. Second malignant neoplasm risk after craniospinal irradiation in X-ray-based techniques compared to proton therapy. *Australas. Phys. Eng. Sci. Med.* 2019;42(1): 201–209.
15. ClinicalTrials.gov. Proton Craniospinal irradiation with bone sparing to decrease growth decrement from radiation. https://clinicaltrials.gov/ct2/show/NCT03281889 (11 Jun 2020, date last accessed)
16. Tansho R, Takada Y, Kohno R et al. Experimental verification of dose calculation using the simplified Monte Carlo method with an improved initial beam model for a beam-wobbling system. *Phys. Med. Biol.* 2013;58:6047–64.
17. Hoeben BA, Carrie C, Timmermann B et al. Management of vertebral radiotherapy dose in paediatric patients with cancer: Consensus recommendations from the SIOPE radiotherapy working group. *Lancet Oncol.* 2019;20(3): e155–e166.
18. Moyers MF, Miller DW, Bush DA et al. Methodologies and tools for proton beam design for lung tumors. *Int. J. Radiat. Oncol. Biol. Phys.* 2001;49(5): 1429–38.
19. Schneider U, Besserer J, Mack A. Hypofractionated radiotherapy has the potential for second cancer reduction. *Theor. Biol. Med. Model.* 2010;7:4.
20. Schneider U, Kaser-Hotz B. Radiation risk estimates after radiotherapy: Application of the organ equivalent dose concept to plateau dose-response relationships. *Radiat. Environ. Biophys.* 2005;44(3): 235–9.
21. Schneider U, Kaser-Hotz B. A simple dose-response relationship for modeling secondary cancer incidence after radiotherapy. *Z. Med. Phys.* 2005;15(1): 31–7.
22. Schneider U, Zwahlen D, Ross D et al. Estimation of radiation-induced cancer from three-dimensional dose distributions: Concept of organ equivalent dose. *Int. J. Radiat. Oncol. Biol. Phys.* 2005;61(5): 1510–5.
23. Hall EJ, Wuu CS. Radiation-induced second cancers: The impact of 3D-CRT and IMRT. *Int. J. Radiat. Oncol. Biol. Phys.* 2003;56(1): 83–8.
24. Schneider U. Mechanistic model of radiation-induced cancer after fractionated radiotherapy using the linear-quadratic formula. *Med. Phys.* 2009;36(4): 1138–43.
25. Preston DL, Pierce DA, Shimizu Y et al. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. *Radiat. Res.* 2004;162(4): 377–89.
26. Preston DL, Ron E, Tokuoka S et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiat. Res.* 2007;168(1): 1–64.

27. Schneider U, Walsh L. Cancer risk estimates from the combined Japanese A-bomb and Hodgkin cohorts for doses relevant to radiotherapy. *Radiat. Environ. Biophys.* 2008;47: 253–63.
28. National Research Council. *High Risks from Exposure to Low Levels of Ionizing Radiation. BEIR VII Phase 2(2006)*. Washington DC: The National Academics Press, 2006.
29. *The 2007 Recommendations of the International Commission on Radiological Protection*. ICRP publication 103. Annals of the ICRP 2007;37(2–4):1–332.
30. Kumazawa S, Numakunai T. a new theoretical analysis of occupational dose distributions indicating the effect of dose limits. *Health Phys.* 1981;41(3): 465–475.
31. Athiyaman H, Mayilvaganan A, Chougule A et al. Estimation of radiation-induced second cancer risk associated with the institutional field matching craniospinal irradiation technique: A comparative treatment planning study. *Rep Pract Oncol Radiother.* 2019;24(5): 409–420.
32. Koshy M, Paulino AC, Mai WY et al. Radiation-induced osteosarcomas in the pediatric population. *Int. J. Radiat. Oncol. Biol. Phys.* 2005;63(4): 1169–74.
33. Tucker MA, D'Angio GJ, Boice JD Jr et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. *N. Engl. J. Med.* 1987;317(10): 588–93.
34. Stoker JB, Grant J, Zhu XR et al. Intensity modulated proton therapy for craniospinal irradiation: Organ-at-risk exposure and a low-gradient junctioning technique. *Int. J. Radiat. Oncol. Biol. Phys.* 2014;90(3): 637–44.
35. Schneider U, Hälg R. The impact of neutrons in clinical proton therapy. *Front. Oncol.* 2015;5:235.