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Evaluating Intensity Modulated Proton Therapy relative to Passive Scattering Proton Therapy for Increased Vertebral Column Sparing in CSI in Growing Pediatric Patients

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Abstract

Purpose—At present, proton craniospinal irradiation (CSI) for growing children is delivered to the whole vertebral body (WVB) to avoid asymmetric growth. We aim to demonstrate the feasibility and potential clinical benefit of delivering vertebral body sparing (VBS) versus WVB CSI with passively scattered (PS) and intensity modulated proton therapy (IMPT) in growing children treated for medulloblastoma.

Methods—Five plans were generated for medulloblastoma patients, previously treated with CSI PS proton radiation therapy (PRT): (a) single posterior-anterior (PA) PS field covering the WVB (*PS-PA-WVB*), (b) single PA PS field including only the thecal sac in the target volume (*PS-PA-VBS*), (c) single PA IMPT field covering the WVB (*IMPT-PA-WVB*), (d) single PA IMPT field, target volume including thecal sac only (*IMPT-PA-VBS*) and (e) two posterior-oblique (-35° , 35°) IMPT fields, target volume including thecal sac only (*IMPT2F-VBS*). For all cases, 23.4Gy(RBE) was prescribed to 95% of the spinal canal. Dose, LET and variable-RBE-weighted dose distributions were calculated for all plans using the TOPAS Monte Carlo system.

Results—IMPT VBS techniques spared efficiently the anterior vertebral bodies (AVB), even when accounting for potential higher variable RBE predicted by linear energy transfer (LET) distributions. Assuming $RBE=1.1$, $V10Gy(RBE)$ decreased from 100% for the WVB techniques to 59.5–76.8% for the cervical, 29.9–34.6% for the thoracic and 20.6–25.1% for the lumbar, and $V20Gy(RBE)$ decreased from 99.0% to 17.8–20.0% for the cervical, 7.2–7.6% for the thoracic and 4.0–4.6% for the lumbar AVB when IMPT VBS techniques were applied. Corresponding values for the PS VBS technique were higher.

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Conclusions—Advanced proton techniques may sufficiently reduce the dose to the vertebral body and allow for vertebral column growth for children with CNS tumors requiring CSI. This holds even when considering variable RBE values. A clinical trial is planned for VBS to the thoracic and lumbosacral spine in growing children.

Keywords

proton radiation; pencil beam scanning; cranio-spinal irradiation; robust optimization

INTRODUCTION

Excellent cure rates for pediatric brain tumor patients have prompted efforts to reduce treatment-related side effects while maintaining tumor control. Craniospinal irradiation (CSI) is an essential part of curative treatment for pediatric cancer cases, mainly medulloblastoma, but it carries risks of morbidity, especially to growing and developing tissues (1–3).

Although the CSI target volume is the whole brain and thecal sac, the entire vertebral column is also “targeted” in growing children in order to avoid risk of spinal deformity related to asymmetric dose across the vertebral body. Studies of children receiving radiation for abdominal and paraspinal tumors have demonstrated that asymmetric irradiation of the vertebral bodies from left to right can result in scoliosis, and that the magnitude of this effect is related to the radiation dose received (4–6). Due to uncertainties in range prediction (7), current proton radiation planning techniques when targeting the thecal sac only typically involve treating at least the posterior half of the vertebral body to full dose and do not provide the ability to spare enough of the vertebral growth plates from doses expected to induce growth impairment without compromising the dose coverage to the thecal sac. The degree to which the vertebral growth plates must be spared in order to prevent a clinically significant lordosis is not known and it is likely impacted by several patients and treatment related factors. Consequently, most radiation oncologists prefer to include the entire vertebral body and growth plate in the treatment volume for growing children and uniformly inhibit growth rather than risk inducing lordosis from radiation dose asymmetry anterior to posterior. Yuh, et al published early results on the treatment of three young patients treated with CSI with a single posteroanterior beam direction using three matched fields along the superior-inferior direction, with the beam stopping just beyond the thecal sac (8). The authors reported favorable early outcomes as minimal effects on blood counts were reported for these children and they experience less nausea, decreased appetite and odynophagia than would be expected for CSI. Long-term outcomes, including the impact on growth, have not yet been reported (8, 9).

If advanced radiation delivery techniques could spare the vertebral growth plates, patients receiving CSI treatment may be able to avoid such side effects. Previous studies have demonstrated that the impact of radiation on growth is dependent on both the dose of radiation received and the age of the patient (1, 2, 4, 5, 10, 11). At birth, each developing vertebral body contains three ossification centers that fuse during childhood (5–8 years of age). In addition, five secondary ossification centers develop during puberty, and it is the

epiphyseal plates at the superior and inferior margin of the vertebral body which contribute to vertebral body height in the pubescent and post-pubescent child (12). Dose effect data has demonstrated that a dose threshold of approximately 10–15 Gy(RBE) is required for radiation associated growth impairment, and a steep dose-effect relationship exists for doses between 15–20 and 35 Gy(13–15). A variety of factors, such as age, growth potential and other treatment (surgery or chemotherapy) may influence the severity of radiation-induced abnormalities in bone growth (13), further complicating the dose-effect relationship in these cases. Delivering CSI treatment while limiting the dose to the central vertebral body, containing the epiphyseal growth plates, to less than 15 Gy could minimize radiation induced growth inhibition.

Proton radiation therapy (PRT) allows for reduced entrance dose and no exit dose compared to conventional photon therapy, which, when used for CSI treatment, significantly improves dose-sparing of organs anterior to the vertebral bodies (16, 17). It may seem that proton therapy could be easily designed to treat only the thecal sac with vertebral body sparing. However, the complexity of the growing vertebra (4, 18, 19) and the setup and proton range uncertainties precludes such a simple treatment approach. Setup and range uncertainties can lead to an increase in the PTV margin of 3 to 5mm if robust optimization techniques are not used. Consequently, current proton therapy planning techniques still include the whole vertebral body (WVB) in the target volume for skeletally immature children and thus provide no current benefit over photon therapy with respect to vertebral body dose and potential growth inhibition. Late side effects caused by irradiation of organs anteriorly to the spinal cord are rare and may take many years to present, which poses a challenge to ascertaining a benefit for protons when measuring patient outcomes, since patients must be closely followed for many years. Modifying CSI technique to allow pediatric patients to reach full height would be a clear and easily measurable benefit of proton CSI over photon treatment.

Intensity-modulated proton therapy (IMPT) using pencil beam scanning (PBS) is a proton treatment planning and delivery method that allows for increased dose conformity and increased degrees of freedom in dose shaping capabilities. Additionally, it allows for larger treatment field sizes and may constitute a more robust delivery technique for CSI treatment compared to passive scattering (PS), which, due to field size limitations, requires longitudinal field conjunctions for CSI treatment, which are potentially sensitive to set-up errors (20, 21).

The purpose of the current study was to evaluate the feasibility of a vertebral body sparing (VBS) CSI delivery technique utilizing IMPT and the level of achievable dose sparing to the vertebral bodies, while maintaining dose coverage to the thecal sac, compared to the currently clinical standard of PS PRT, considering both dosimetric and biological indices. This study can then guide a potential clinical study on the vertebral body sparing techniques.

METHODS AND MATERIALS

Patient Imaging and Contouring

Two patients, ages 8 & 11 previously treated for medulloblastoma at our institution with CSI PS PRT to the thecal sac and WVB, were selected for this study. The patients had undergone computed tomography (CT) imaging (slice thickness of 3.75mm) in the prone position. For the purpose of this vertebral-sparing study, a new thecal sac clinical target volume (CTV) was contoured including the spinal canal as seen on CT extending laterally to encompass the cerebrospinal fluid extension to the spinal ganglia. Organs at risk (OARs) outlined for this study included the vertebral body, thyroid gland, esophagus, liver, kidneys, and small bowel. For dose reporting and analysis, the vertebral body contour was further divided into an anterior and posterior vertebral body component, and each one of them into three additional components: cervical (C-spine), thoracic (T-spine) and lumbar (L-spine). Figure 1 depicts the contour for clinical target volume (red) and anterior (blue) and posterior (purple) vertebral body.

Treatment planning

For PS delivery, a range compensator is utilized to conform the dose distribution to the distal edge of the target volume, while apertures are used in order to tightly conform the lateral penumbra to the target edge. In PBS delivery, appropriate beam spot arrangement (energy and position) is determined by IMPT treatment planning optimization to produce a dose distribution that will conform to both the distal and proximal edges of the target.

In addition to the original PS treatment plan created using the commercial TPS XiO (Elekta, city, state/country), an additional PS and three IMPT plans were generated. IMPT plans were optimized using the ASTROID TPS, developed in-house for IMPT treatment planning. A virtual PBS delivery system was used for the treatment planning, with spot size (sigma in air at isocenter) ranging from 2.2 to 5.6 mm for corresponding proton beam energies ranging from 230 to 60 MeV.

For the PBS plans, full IMPT inverse optimization was utilized. For the PS plan the clinical range uncertainty definition of 3.5% plus 1mm was used (7), which is a common practice at the majority of centers. Since our PBS TPS does not offer the possibility to define the range uncertainty the same way, for the IMPT plans a uniform volume extension of 2mm was used as the planning target volume (PTV). This was estimated as the range uncertainty (using 3.5%+1mm) corresponding to the maximum pencil beam energy used for each field, averaged over the length of the target volume. Two couch positions were assumed in the spino-caudal direction for the IMPT plans; the junction of the fields in this direction was managed automatically by the optimizer by allowing for 2–4cm overlap of the fields, depending on the patient size.

Five plans are included in this study for each patient:

- a. PS-PA-WVB (Original plan): For this plan a single PS posterior-anterior (PA) field direction covering the WVB was utilized, which is the standard practice for CSI treatment at our institution.

- b. PS-PA-VBS: A single PA direction PS field direction covering only the thecal sac PTV.
- c. IMPT-PA-WVB: A single PA direction IMPT field covering the thecal sac and WVB was created for comparison with the standard PS-PA plan.
- d. IMPT-PA-VBS: A single PA direction IMPT field covering only the thecal sac PTV.
- e. IMPT2F-VBS: Two posterior-oblique IMPT fields, at -35° and 35° (0° corresponds to the PA beam direction) covering the thecal sac PTV only.

Monte Carlo dose calculations

Patient (original CT image and contoured structures) and beam geometry information were imported into the TOPAS (TOOl for PArticle Simulation – v2) Monte Carlo (MC) system (22), for each treatment plan. The MC-calculated dose distributions of all treatment plans were normalized to the same target coverage: at least 95% of the CTV (thecal sac) to receive 100% of the prescription dose ($D_{95\%} = 23.4 \text{ Gy[RBE]}$ and $V_{100\%} = 95\%$). Normalization factors ranged from 1.7% to 4.3%. The results are reported with reference to the normalized MC-based calculated physical dose.

Monte Carlo calculation of linear energy transfer (LET) and variable-RBE-weighted dose

While for the treatment planning process the clinically used constant RBE value of 1.1 was used in the dose calculation, it is generally accepted that the RBE value is increasing at the end of proton range, due to the increase in LET. In order to study the potential consequences of an increasing RBE at the end of range, dose and dose-averaged LET (LET_d) distributions were scored on a voxel by voxel basis (23). To estimate the potential clinical implications associated with increased LET values at the anterior part of the treatment fields, variable RBE and RBE-weighted dose distributions were calculated. The model by McNamara et al. (24) was employed for this purpose, which is based on the standard linear-quadratic dose-response formalism, assuming a linear relationship between LET and RBE for a given dose, with the slope depending on the α/β ratio of the tissue. An α/β ratio of 2.5 Gy was used for the vertebral body (25) and 28 Gy for the thecal sac target volume (26). The normalized MC dose distributions from the previous step were used for the variable-RBE calculation and the variable-RBE-weighted dose distribution was obtained by multiplying the physical dose by the RBE value in each voxel.

Plan Evaluation

Treatment plan comparisons were performed based on target coverage and OAR sparing. Two-dimensional dose, LET and variable-RBE-weighted dose distributions were utilized, along with the corresponding dose or LET volume histograms. Specific dose-volume indices were employed for plan evaluation and comparison such as the target volume covered by 22.2 Gy(RBE) dose level ($V_{95\%}$), the vertebral body volume covered by 10, 15 and 20 Gy(RBE) dose levels ($V_{10\text{Gy}}$, $V_{15\text{Gy}}$ and $V_{20\text{Gy}}$ respectively). Dose conformity was also evaluated and compared among the different plans based on the conformity index (27):

$$CI = \frac{TV_{PIV}^2}{TV \times PIV}, \quad (1)$$

where TV_{PIV} is the volume of the target covered by the prescription isodose (PI), TV is the target volume and PIV is the prescription isodose volume.

RESULTS

Two-dimensional dose distributions for C-spine, T-spine and L-spine regions of the patient body for one of the cases are presented in figure 2 for all five techniques, under the assumption of constant RBE=1.1. Table 1 summarizes dose, LET and variable-RBE indices for the different planning techniques averaged over both patients.

Dose-comparison between PS-PA-WVB and IMPT-PA-WVB plans using RBE=1.1: Whole Vertebral Body Irradiation

Better dose conformity with the IMPT-PA-WVB technique compared to PS-PA-WVB technique is demonstrated by the reduced dose posteriorly of the vertebral body in the IMPT-PA-WVB plan for the lumbar and cervical levels of the vertebral column (figure 2 – 1st and 3rd columns). Similar coverage by the 10, 15 and 20 Gy(RBE) isodose lines was observed between IMPT-PA-WVB and PS-PA-WVB CSI plans for most parts of the vertebral bodies (Table 1), while the skin dose was reduced with the IMPT-PA-WVB approach, especially for the C- and L-spine regions (figure 2 – 1st and 2nd columns). Additionally, significant dose decrease was observed for the esophagus, for which the mean dose, averaged over the patients, was reduced from 11.5Gy(RBE) for the PS-PA-WVB plan to 6.9Gy(RBE) for the IMPT-PA-WVB plan.

Dose comparison between WVB and VBS IMPT plans using RBE=1.1

Two-dimensional dose distributions of the C-spine, T-spine and L-spine regions for the VBS CSI techniques (PS-PA-VBS, IMPT-PA-VBS and IMPT2F-VBS) are presented in the 2nd, 4th and 5th columns in figure 2. The PS-PA-VBS plan resulted in better sparing of the anterior vertebral column compared to the original PS-PA-WVB plan, but minor differences were noticed concerning the posterior vertebral column sparing. Both IMPT VBS plans resulted in significantly better sparing of both the anterior and posterior vertebral column compared to the WVB plans (PS-PA-WVB and IMPT-PA-WVB) and the PS VBS plan. IMPT2F-VBS generally resulted in better sparing of the posterior vertebral column (mean dose was 18.6Gy(RBE), compared to 19.8Gy(RBE) for IMPT-PA-VBS - Table 1), while the IMPT-PA-VBS plan resulted in better sparing of the anterior spinal column. The V10Gy(RBE) for the thoracic anterior vertebral bodies (AVBs) decreased from 100% for the WVB plans to 48.1% for PS-PA-VBS, 29.1% for IMPT-PA-VBS and 34.6% for IMPT2F-VBS plans, and for the lumbar AVBs to 36.7% for PS-PA-VBS, 20.6% for IMPT-PA-VBS and 25.1% for IMPT2F-VBS plans. Similarly, V20Gy(RBE) for the thoracic AVBs decreased from 98.2% (IMPT-PA-WVB) to 14.4% for IMPT-PA-VBS and 13.8% for IMPT2F-VBS plans, and for the lumbar AVBs from 95.2% (IMPT-PA-WVB) to 7.2% (IMPT-PA-VBS) and 7.6% (IMPT2F-VBS). Corresponding decreases for the cervical AVBs

were smaller (Table 1). Dosimetric analysis for other OARs revealed that the most significant dose decrease was observed for the esophagus, for which the mean dose was further reduced from 6.9Gy(RBE) (IMPT-PA-WVB plan) to 0.2Gy(RBE) for the PS-PA-VBS, 0.5Gy(RBE) for the IMPT-PA-VBS and 1.8Gy(RBE) for the IMPT2F-VBS plans. The IMPT VBS plans result in better dose conformity over the PS-PA-VBS one: the CI for IMPT-PA-VBS and IMPT2F-VBS was 0.43 and 0.48 respectively versus 0.14 for PA-PA-VBS. However, beam delivery time for IMPT2F-VBS would be almost twice as long compared to IMPT-PA-VBS.

Variable RBE Effect on Proton Dose Distributions based on Linear Energy Transfer (LET) Distributions

Figure 3 shows the results of fixed and variable RBE-weighted dose and LET calculations for the IMPT-PA-VBS plan of one of the patients. Increased LET values at the end of range result in more than 10% (2.34 out of 23.4 Gy(RBE) prescription dose) increase in variable-RBE-weighted dose, compared to the constant-RBE-dose distributions.

Figure 4 displays the dose and LET volume histograms for all plans for the thecal sac and the whole vertebral body. Accounting for variable-RBE results in dose increase in the vertebral body by more than 10%, for all five techniques. As shown in Table 1, a significant increase in volume coverage by the 10, 15 and 20 Gy(RBE) isodose lines is noticed for all VBS techniques when going from constant (columns 5, 9 and 11 in Table 1) to variable (columns 6, 10 and 12) RBE-weighted dose. The thoracic AVB volume covered by V20Gy(RBE) increased from 29.3% to 42.5% for the PS-PA-VBS plan, from 7.2% to 20.1% for the IMPT-PA-VBS plan and from 7.6% to 21.0% for the IMPT2F-VBS plan, assuming variable-RBE-weighted dose. Similar differences were noticed for the cervical and lumbar AVBs for all 10, 15 and 20Gy(RBE) isodose levels. Significant increase in the V_{20Gy} of the posterior vertebral body was also observed. Accounting for variable-RBE also lead to a dose increase in the esophagus for the WVB plans, however the corresponding increase for the VBS plans was less noticeable due to the very low physical dose for these plans. The IMPT VBS plans still resulted in better dose conformity compared to the PS-PA-VBS plan (0.55–0.57 versus 0.17).

DISCUSSION AND CONCLUSION

Current proton spinal irradiation techniques, while sparing organs anteriorly to the vertebral column, still irradiate the vertebral bodies and thus do not offer any benefit for growth or hematopoietic sparing. In this study we evaluate the dosimetric benefit of VBS techniques, utilizing PS and IMPT delivery methods - including range uncertainty margins - and the advanced dose calculation accuracy of MC, and the effect of the increased LET and RBE values at the end of range.

We demonstrate that increased dose conformity can be achieved with VBS techniques, sparing a significant amount of the vertebral bony elements from radiation doses that would cause growth impairment. Compared to the PS-PA-VBS technique, IMPT techniques achieved decreased volumetric coverage of both the anterior and posterior vertebral bodies for the 10, 15 and 20Gy(RBE) isodose lines, due to the dose conforming to both distal and

proximal edges of the tumor and the sharp dose fall-off in the distal edge of the pencil beams. Multiple beam angles further decreased the dose received by the posterior vertebral bodies and may offer the possibility for more robust plans. The thoracic and lumbar sections of the anterior vertebral bodies seem to be mostly benefited by the VBS techniques.

When accounting for variable RBE, an increase in the vertebral body dose by more than 10% was noticed, for all delivery techniques. This should be considered during treatment planning for CSI patients when trying to spare the vertebral body growth plate and limit the dose to the thecal sac. Accounting for a variable RBE may have significant impact when assessing the benefits of planning techniques where only the thecal sac is used as a target volume.

Limiting the vertebral body volume receiving 20Gy(RBE) or even 15 and 10Gy(RBE) may reduce the adverse effects of radiation to the patient's growth. Additional benefits to vertebral body sparing other than the potential to reach full height are likely. Spinal irradiation impacts hematopoietic cell production and avoiding radiation of the spine will likely result in a decreased need for transfusions and may improve tolerance of chemotherapy. In addition, it is very difficult to harvest stem cells following spinal irradiation. Sparing of this bone marrow may allow for stem cell harvest following CSI. Late effects of decreased bone density, osteopenia, orthopedic problems, and fracture are also potential sequelae of vertebral irradiation. Obesity is also a recognized problem in children receiving radiation to the spine and with obesity come numerous additional medical problems.

In conclusion, our study demonstrates the possibility of sparing both anterior and posterior vertebral bodies by utilizing thecal sac only IMPT irradiation techniques for children with CNS tumors requiring CSI, potentially allowing for vertebral column growth. Considering variable RBE values results in increased spine doses, although the vertebral body sparing remains significant even in this case. Clinical trials applying VBS CSI irradiation techniques should be the next step, in an effort to clinically evaluate the benefit. The VBS technique could initially be applied only to the lumbar or thoracic spine, where the dosimetric sparing is most pronounced. Ideal initial candidates may include children closer to full height and/or those receiving low CSI doses (23.4 Gy(RBE)).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

MC calculation of LET

Using the TOPAS Monte Carlo calculation system the dose (dose-to-water) and the corresponding dose averaged LET (LET_d) values, in units of keV/ μm per unit density tissue, were scored in a voxel-by-voxel basis on the clinical dose calculation grid. The LET_d is given by equation (1):

$$LET_d(v) = \frac{\sum_{events} dE \cdot (dE/dx) \cdot \frac{1}{\rho}}{\sum_{events} dE} \quad (1)$$

where dE is the energy deposition associated with a particle's energy loss, dx the particle's step length and ρ the tissue density of voxel (v).

RBE and RBE-weighted dose distribution

Utilizing the MC dose and LET values, the RBE value was calculated for each voxel using the McNamara model (equation 2):

$$RBE \left[D_p, \left(\frac{\alpha}{\beta} \right)_x, LET_d \right] = \frac{1}{2D_p} \left(\sqrt{\left(\frac{\alpha}{\beta} \right)_x^2 + 4D_p \left(\frac{\alpha}{\beta} \right)_x \left(0.999064 + \frac{0.35605}{(\alpha/\beta)_x} LET_d \right) + 4D_p^2 \left(1.1012 - 0.0015724 \sqrt{(\alpha/\beta)_x LET_d} \right)^2} - \left(\frac{\alpha}{\beta} \right)_x \right)$$

where D_p is the physical dose for each voxel, as calculated by TOPAS, LET_d is the corresponding dose-averaged LET value, and $(\alpha/\beta)_x$ is the α/β ratio for each structure where the RBE and RBE-weighted dose is calculated.

The RBE-weighted dose is then calculated by multiplying the above calculated RBE value by the dose in voxel-by-voxel basis.

This study investigates the feasibility and potential clinical benefit of delivering vertebral body sparing (VBS) versus whole vertebral body craniospinal irradiation (CSI) with passive scattering and intensity modulated proton therapy in growing children treated for medulloblastoma. VBS techniques spare efficiently the anterior vertebral bodies and may allow for vertebral column growth for children with CNS tumors requiring CSI, even when considering variable RBE values.

Figure 1. Vertebral body contouring including the clinical target volume (red line), anterior (blue) and posterior (purple) vertebral body.

Figure 2.

Two-dimensional dose distributions of (1st column) PS-PA-WVB, (2nd column) PS-PA-VBS, (3rd column) IMPT-PA-WVB, (4th column) IMPT-PA-VBS and (5th column) IMPT2F-VBS plans for (top row) C-spine, (middle row) T-spine and (bottom row) L-Spine regions. PS: passive scattering; IMPT: intensity modulated proton therapy; PA: posterior anterior; 2F: two-field; WVB: whole vertebral body; VBS: vertebral body sparing;

Figure 3.

IMPT-PA-VBS planning arrangement for a C-spine, T-spine and L-Spine regions: Constant RBE weighted dose (left), LET (center) and variable RBE weighted dose (right) distributions. Light blue contour defines thecal sac structure and dark blue contour defines full CTV structure as used for the whole vertebral body (WVB) plans.

Figure 4.

Constant-RBE dose (top), LET (middle) and variable-RBE-weighted dose (bottom) volume histograms for one of the patients. Solid lines represent the volume histograms for the thecal sac and the dotted lines for the whole vertebral body structures. Each color represent a different planning technique.

Table 1

Dose (constant RBE), LET and variable RBE-weighted dose indices, averaged over patients under study

		PS-PA-WVB		PS-PA-VBS		IMPT-PA-WVB		IMPT-PA-VBS		IMPT2F-VBS	
		RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE
Thecal Sac ($\alpha/\beta=28\text{Gy}$)	Mean Dose	23.9	22.6	24.2	23.0	24.0	22.7	24.3	23.3	24.4	23.3
	V95%	99.4%	90.6%	99.1%	95.5%	99.8%	91.6%	99.4%	96.4%	99.8%	94.9%
	V100%	95.1%	3.8%	95.0%	22.1%	95.0%	2.3%	95.0%	40.7%	95.0%	44.3%
	Mean LET	2.6	2.6	3.3	3.3	2.5	2.5	3.8	3.8	3.4	3.4
	PIV			704.7	517.0			222.6	166.5	208.9	159.1
WB+Thecal Sac ($\alpha/\beta=2.5\text{Gy}$)	TV			95.7	95.7			95.7	95.7	95.7	95.7
	CI (95%)			0.14	0.17			0.43	0.55	0.48	0.57
	Mean Dose	23.6	26.2	19.2	22.4	23.8	26.4	15.9	18.8	16.3	19.1
	V10Gy	99.2%	99.3%	81.5%	84.5%	100.0%	100.0%	72.0%	76.9%	74.9%	80.3%
	V15Gy	98.6%	98.9%	78.1%	81.9%	100.0%	100.0%	63.8%	69.8%	62.7%	69.9%
Anterior WVB	V20Gy	97.3%	98.2%	73.2%	78.8%	99.4%	100.0%	49.3%	59.3%	46.2%	56.6%
	Mean LET	3.0	3.0	4.8	4.8	2.8	2.8	5.3	5.3	4.4	4.4
	Mean Dose	23.8	27.2	10.2	13.8	23.6	27.0	6.3	9.0	7.7	10.7
	V10Gy	100.0%	100.0%	45.5%	53.4%	100.0%	100.0%	27.4%	38.4%	32.9%	44.7%
Whole	V15Gy	99.9%	100.0%	37.6%	47.0%	99.8%	100.0%	16.3%	27.4%	19.2%	31.3%
	V20Gy	99.0%	99.6%	27.8%	40.3%	97.3%	99.9%	6.3%	17.8%	6.9%	19.5%
	Mean LET	3.6	3.6	7.9	7.9	3.6	3.6	9.2	9.2	7.0	7.0
	Mean Dose	22.4	25.7	19.2	24.5	23.5	27.6	12.4	16.9	14.6	19.0
	V10Gy	100.0%	100.0%	90.1%	96.6%	100.0%	100.0%	59.5%	76.1%	76.8%	92.5%
C-Spine	V15Gy	98.8%	99.7%	79.0%	91.2%	99.7%	100.0%	39.0%	59.0%	49.1%	72.6%
	V20Gy	87.9%	95.2%	61.3%	82.4%	96.0%	99.9%	17.8%	41.2%	20.0%	47.7%
	Mean LET	3.6	3.6	6.3	6.3	4.3	4.3	7.0	7.0	5.8	5.8
	Mean Dose	23.9	27.6	10.8	14.7	23.2	26.7	6.7	9.6	8.2	11.4
	V10Gy	100.0%	100.0%	48.1%	56.8%	100.0%	100.0%	29.9%	41.1%	34.6%	47.4%
T-Spine	V15Gy	100.0%	100.0%	39.7%	49.7%	99.7%	100.0%	18.3%	30.1%	20.4%	33.1%

		PS-PA-WVB		PS-PA-VBS		IMPT-PA-WVB		IMPT-PA-VBS		IMPT2F-VBS	
		RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE
	V20Gy	99.8%	100.0%	29.3%	42.5%	95.2%	99.8%	7.2%	20.1%	7.6%	21.0%
	Mean LET	3.8	3.8	8.0	8.0	3.8	3.8	8.9	8.9	6.8	6.8
	Mean Dose	23.8	27.1	8.3	11.4	24.1	27.2	5.0	7.3	6.2	8.8
	V10Gy	100.0%	100.0%	36.7%	43.9%	100.0%	100.0%	20.6%	30.6%	25.1%	35.5%
	V15Gy	100.0%	100.0%	29.8%	38.1%	99.9%	100.0%	11.2%	20.5%	14.0%	23.8%
L-Spine	V20Gy	99.8%	100.0%	21.6%	32.2%	99.5%	100.0%	4.0%	12.4%	4.6%	14.4%
	Mean LET	3.4	3.4	8.0	8.0	3.3	3.3	9.8	9.8	7.3	7.3
	Mean Dose	23.6	25.7	23.5	25.9	23.7	25.6	19.8	21.9	18.6	20.6
	V10Gy	99.5%	99.6%	99.2%	99.4%	100.0%	100.0%	94.1%	95.6%	94.1%	95.9%
Whole	V15Gy	98.8%	99.1%	98.4%	98.8%	100.0%	100.0%	86.3%	89.3%	77.6%	82.9%
	V20Gy	97.2%	98.2%	95.4%	97.5%	99.2%	99.8%	61.0%	72.1%	47.8%	60.2%
	Mean LET	2.5	2.5	2.8	2.8	2.4	2.4	2.6	2.6	2.5	2.5
	Mean Dose	23.7	26.0	23.3	25.6	23.7	25.9	20.8	23.1	20.0	22.2
	V10Gy	100.0%	100.0%	99.4%	99.6%	100.0%	100.0%	97.2%	98.1%	97.1%	98.2%
C-Spine	V15Gy	99.8%	99.9%	98.3%	98.8%	100.0%	100.0%	90.7%	94.0%	87.5%	91.8%
	V20Gy	98.6%	99.3%	95.5%	97.2%	99.8%	100.0%	69.6%	80.6%	61.1%	74.6%
	Mean LET	2.6	2.6	2.7	2.7	2.5	2.5	2.8	2.8	2.7	2.7
	Mean Dose	23.1	25.1	22.9	25.1	22.8	24.6	18.7	20.4	16.9	18.6
	V10Gy	98.5%	98.6%	99.1%	99.3%	99.0%	99.2%	92.5%	94.0%	85.5%	88.0%
T-Spine	V15Gy	98.2%	98.4%	98.6%	99.0%	98.6%	98.9%	81.0%	84.4%	63.8%	68.4%
	V20Gy	93.8%	96.6%	86.5%	91.2%	90.7%	93.9%	48.7%	57.8%	38.7%	48.5%
	Mean LET	2.5	2.5	2.7	2.7	2.3	2.3	2.3	2.3	2.3	2.3
	Mean Dose	23.3	25.2	23.2	25.7	23.7	25.6	19.3	21.5	18.0	20.0
	V10Gy	98.7%	99.1%	98.1%	98.5%	100.0%	100.0%	92.4%	94.3%	90.2%	92.9%
L-Spine	V15Gy	97.1%	97.7%	96.6%	97.4%	100.0%	100.0%	82.8%	86.9%	73.3%	79.5%
	V20Gy	94.5%	95.8%	94.1%	95.7%	98.8%	99.7%	56.5%	68.4%	44.8%	56.4%
	Mean LET	2.3	2.3	2.9	2.9	2.2	2.2	2.8	2.8	2.6	2.6
	Mean Dose	23.3	25.2	23.2	25.7	23.7	25.6	19.3	21.5	18.0	20.0

		PS-PA-WVB		PS-PA-VBS		IMPT-PA-WVB		IMPT-PA-VBS		IMPT2F-VBS	
		RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE	RBE = 1.1	Variable RBE
Thyroid ($\alpha/\beta = 3.0$ Gy)	Other OARs										
	Mean Dose	1.2	2.1	0.2	0.2	1.5	2.5	0.1	0.1	0.4	0.7
	V10Gy	1.5%	5.1%	0.0%	0.2%	0.5%	2.2%	0.0%	0.0%	0.0%	0.0%
	Median Dose	0.3	0.6	0.1	0.1	1.0	1.8	0.1	0.1	0.3	0.5
Esophagus ($\alpha/\beta = 3.0$ Gy)	Mean LET	7.5	7.5	6.9	6.9	8.9	8.9	8.8	8.8	8.0	8.0
	Mean Dose	11.5	16.5	0.2	0.4	6.9	10.3	0.5	0.8	1.8	2.6
	V10Gy	57.8%	76.4%	0.0%	0.0%	18.9%	52.0%	0.0%	0.0%	0.0%	0.0%
	Median Dose	11.6	17.3	0.1	0.2	6.7	10.3	0.1	0.1	1.7	2.5
L Lung ($\alpha/\beta = 3.0$ Gy)	Mean LET	9.0	9.0	7.2	7.2	8.2	8.2	10.5	10.5	6.3	6.3
	Mean Dose	2.3	3.0	2.2	2.8	2.7	3.4	1.1	1.5	1.0	1.3
	D10	9.7	13.0	9.9	12.5	10.3	13.1	3.8	5.3	3.0	4.2
	D50	11.6	17.3	0.1	0.2	6.7	10.3	0.1	0.1	1.7	2.5
R Lung ($\alpha/\beta = 3.0$ Gy)	Mean LET	5.4	5.4	5.4	5.4	5.0	5.0	5.8	5.8	5.7	5.7
	Mean Dose	3.0	3.9	2.2	2.9	3.3	4.2	1.2	1.7	1.0	1.4
	D10	13.7	17.7	9.6	12.9	13.2	16.7	4.0	5.7	3.0	4.3
	D50	11.6	17.3	0.1	0.2	6.7	10.3	0.1	0.1	1.7	2.5
Heart ($\alpha/\beta = 3.0$ Gy)	Mean LET	5.7	5.7	5.9	5.9	5.4	5.4	6.5	6.5	5.9	5.9
	Mean Dose	0.3	0.5	0.1	0.1	0.6	1.0	0.1	0.1	0.1	0.2
	D10	0.4	0.7	0.1	0.1	1.9	3.2	0.1	0.1	0.3	0.4
	D50	11.6	17.3	0.1	0.2	6.7	10.3	0.1	0.1	1.7	2.5
	Mean LET	6.7	6.7	6.7	6.7	10.5	10.5	11.7	11.7	9.0	9.0

PS: passive scattering; IMPT: intensity modulated proton therapy; PA: posterior anterior; 2F: two-field; WVB: whole vertebral body; VBS: vertebral body sparing; RBE: relative biological effectiveness; LET: Linear energy transfer; PIV: Prescription isodose volume (using the 95% level at this study); TV: Tumor volume; CI: conformity index; WVB: whole vertebral body; C-Spine: cervical spine; T-Spine: thoracic spine; L-Spine: lumbar spine; OARs: organs at risk

V95%: Volume covered by the 95% isodose level, with reference to the prescription dose; V10Gy: volume covered by 10Gy; V15Gy: volume covered by 15Gy; V20Gy: volume covered by 20Gy; CI (95%): conformity index using the 95% isodose level;