To the Editor-In-Chief of Pediatric Blood & Cancer:

We authors would like to introduce our submitted manuscript for review, which is titled: Volumetric De-Escalation and Improved Acute Toxicity with Proton Craniospinal Irradiation Using a Vertebral Body Sparing Technique.

In brief, this is a report of new data from our institution regarding the craniospinal irradiation (CSI) of growing children using a vertebral body sparing proton technique with the purpose of reducing radiation dose to the spinal bone marrow and the upper gastrointestinal tract. A prior case series by MacEwan et al. (PMID 28740935) illustrated the feasibility and long-term safety of this proton technique in the growing spine, and the current report highlights the acute toxicities and compares these to toxicities in a cohort of children treated with photon CSI at our facility. In brief, children treated with vertebral body sparing technique were found to have reduced rates of grade 2+ gastrointestinal toxicity, grade 2+ nausea, and any-grade esophagitis, as well as reduced rates of red blood cell transfusions and grade 4 lymphopenia. These findings overall clinically reflect the dosimetric benefits of vertebral body sparing protons and adds to the growing body of evidence supporting the use of protons for pediatric CSI and highlight the acute gastrointestinal and hematologic differences.

The authors have no conflicts of interest. All authors listed below have contributed in significant and meaningful ways to the manuscript and have reviewed and agreed upon the final version of this manuscript. Three potential reviewers include: Dr. Shannon MacDonald MD, Dr. Torunn Yock MD, and Dr. Thomas Merchant DO PhD.

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TITLE PAGE

FULL TITLE

Volumetric De-Escalation and Improved Acute Toxicity with Proton Craniospinal Irradiation Using a Vertebral Body Sparing Technique

SHORT RUNNING TITLE (MAX 50 CHARACTERS)

Improved Acute Toxicity with VBSpCSI

WORD COUNT

Abstract: 250 words

Main Text: 2479 words

Tables: 2

Figures: 1

Keywords for Indexing:

CNS Tumors

Radiotherapy

Proton therapy

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Abbreviations:

CSI	Craniospinal irradiation
VB	Vertebral body
VBSpCSI	Vertebral body sparing proton craniospinal irradiation
CTV	Clinical target volume
PTV	Planning target volume
DFS	Disease free survival
CSF	Craniospinal fluid
PA	Posterior-Anterior
3DCRT	3D conformal radiotherapy
IMRT	Intensity modulated radiotherapy
VMAT	Volumetric modulated arc therapy
IRB	Institutional review board
CBCT	Cone-beam CT scan
GI	Gastrointestinal
CTCAE	Common Terminology Criteria for Adverse Events
pRBC	Packed red blood cell

ABSTRACT

Purpose:

Craniospinal irradiation (CSI) has historically treated the entire vertebral body (VB) in growing children. Vertebral body sparing proton craniospinal irradiation (VBSpCSI) is a technique which spares the majority of the VB from significant irradiation. This retrospective study reviews the acute toxicity of VBSpCSI compared to photon CSI.

Methods:

Pediatric CSI patients treated between 2008 and 2018 were evaluated. Patients were stratified to the VBSpCSI cohort or the photon cohort and analyzed for acute toxicity profile during treatment and disease-free survival (DFS). Statistical analysis was performed using Kaplan-Meier log rank analysis for DFS and Fisher's exact test for toxicity.

Results:

Twenty-five patients received VBSpCSI and 13 patients received photon CSI. Mean patient age at treatment was 7.5y (range 2 to 16). The cohorts were well-matched with respect to gender, age, and CSI dose. Two-year DFS was similar between cohorts (81% VBSpCSI vs 61% photon, p=0.18). Patients receiving VBSpCSI had lower rates of grade 2+ GI toxicity (24% vs 76.5%, p=0.005), grade 2+ nausea (24% vs 61.5%, p=0.035), and any-grade esophagitis (0% vs 38%, p=0.0026). Patients treated with VBSpCSI had lower red blood cell transfusion rates (21.7% vs 60%, p=0.049) and grade 4+ lymphopenia (33.3% vs 77.8%, p=0.046).

Conclusions:

VBSpCSI in children is a volumetric de-escalation from traditional volumes which irradiate the entire vertebral body. Based on our results, VBSpCSI was associated with less acute gastrointestinal and hematologic toxicity. The study adds to the growing body of evidence supporting the use of protons over photons for pediatric CSI.

MAIN TEXT:

INTRODUCTION

Radiation therapy is an important modality used in the treatment of many pediatric primary central nervous system tumors. In the modern era, craniospinal irradiation (CSI) remains standard for patients with medulloblastoma and other tumors that have a propensity to disseminate in the craniospinal fluid (CSF). Photon CSI is associated with significant exit dose to the anterior structures of the thorax, abdomen, and pelvis. This exit dose is associated with significant acute and late toxicities[1,2].

The concept of reducing exit dose with charged particle CSI is not a novel concept, dating back to 1985 with the use of electrons for CSI at MD Anderson where 15-17MeV electrons were used to reduce anterior dose[3]. However, this fell out of favor due to logistical, technical, and dosimetric obstacles. More recently, proton CSI allows for further sparing of structures beyond the target volume, especially the structures anterior to the vertebral body and the brain anterior to the posterior fossa during the boost phase of treatment. The known dosimetric benefit is leading to a growing body of clinical evidence demonstrating reduced early and late toxicities using protons compared to photons[4-12].

In skeletally immature patients receiving proton CSI, the whole vertebral column is typically included in the clinical target volume (CTV) due to concern for spinal abnormalities after treatment[13,14]. This curtails the full dosimetric advantage of the technique, allowing dose spillage to structures not at risk for disease, including the spinal growth plates, bone marrow, esophagus,

larynx, and pharynx, among others. In contrast, vertebral body sparing proton CSI (VBSpCSI) volumetrically de-escalates the treatment volume by excluding the vertebral bodies from the CTV and allowing the protons to terminate just anterior to the thecal sac, thus maximally sparing anterior structures (Figure 1a, b). A number of recent publications have shown safety of VBSpCSI in skeletally immature patients with extended follow-up[15,16] A prospective multi-institutional single-arm trial is currently ongoing (NCT 03281889) which has a primary endpoint to validate the feasibility of VBSpCSI and secondary endpoints to evaluate growth and spinal changes.

Comparative data regarding acute toxicity differences between photon and proton CSI has been published in adult medulloblastoma patients[17]. Proton patients were found to have significantly less grade 2 nausea and vomiting, as well as esophagitis. Additionally the adult patients receiving VBSpCSI had numerically smaller reductions in hemoglobin, platelets, and white blood cells, all of which were significant although in a non-randomized retrospective comparison[17]. To our knowledge, there is no similar comparison in the pediatric population. In this retrospective single institution study, we report on the acute toxicity profiles of children treated with VBSpCSI at our institution and compared them with children receiving photon CSI.

METHODS AND MATERIALS

Patients

All pediatric patients (age less than 18) at our institution treated with either photon CSI or VBSpCSI between 2008 and 2018 were included in this study. While most patients receiving

CSI had medulloblastoma, we also included non-medulloblastoma patients receiving CSI, as our goal was to evaluate acute toxicities and not disease-specific outcomes. Medulloblastoma patients were categorized as either standard or high risk according to the Children's Oncology Group criteria. Prior to 2014, patients were treated with photon CSI. Once the proton therapy center opened in 2014, most patients were treated with VBSpCSI.

Treatment Planning

All patients were simulated and treated in the supine position with thermoplastic mask immobilization. Three-dimensional planning was done with CT simulation. General anesthesia was used when required.

Proton Technique

All proton patients were treated on the Varian ProBeam Pencil Beam Scanning System and planned using Varian Eclipse. For VBS proton planning, the whole brain was included in the clinical target volume (CTV) and treated with posterior-anterior (PA) intensity-modulated proton beams. A minority of patients required two 5-degree posterior obliques (instead of a single PA beam) to improve lateral brain coverage. Coverage was ensured at the cribriform plate and inferior temporal lobes. Delineation of the boost volumes varied per diagnosis and protocol. The spinal CTV included the entire thecal sac and exiting sacral nerves, which was determined on CT simulation with fused-MRI of the spine whenever feasible. All proton patients were treated with VBS technique irrespective of skeletal maturity. The thecal sac contours included the entire spinal canal and the exiting nerve roots laterally to the lateral edge of the vertebral body.

Inferiorly, contours ended at or near the S2/3 interspace. Beam-specific planning target volumes and robustness evaluation were used to account for distal edge uncertainty and daily setup differences. The superior PA proton beam was matched to the inferior PA proton beam using a gradient match technique. Proton volume boosts were completed using with 2 or 3-beam technique.-

Photon Technique

All photon patients were treated on Varian Linear Accelerators planned using Varian Eclipse. Most photon patients were treated with 3DCRT planning that included posterior beam(s) for the spine field that were matched to lateral angle beams for the brain. Feathering occurred once weekly at the match line. One patient was treated to the spine with volumetric modulated arc therapy (VMAT) technique, partial arcs were used for the spine fields that were matched to lateral angle fields for the brain; one patient treated with intensity modulated radiotherapy (IMRT) to the spine was matched in the same fashion. Posterior fossa volume boosts were completed with VMAT technique in 2 cases and IMRT in the remainder. Alignment verification was completed with daily kV imaging for both techniques. In some cases kilovoltage cone-beam CT (CBCT) was used for alignment of the brain boost.

Dose and Treatment

Patients were treated with a CSI dose of 23.4-36.0 Gy followed by boosts to the posterior fossa and metastatic site volumes. Proton patients were treated in cobalt gray equivalent (CGE). Some patients were given an additional spinal/posterior fossa boost to 39.6 Gy in cases where there

was diffuse disease in the spine. Additional spine boosts to 45-54 Gy were done for areas of bulky spinal disease. Primary site volume boosts dose varied between 54 Gy and 55.8 Gy. Coverage goals were similar between modalities. In the proton cohort the goal was to have 95% coverage to the CTV. Beam specific planning target volumes (PTVs) were created to ensure coverage and robustness analysis was performed in the proton cohort. In the photon cohort the goal was to have 95% coverage to the PTVs. Chemotherapy varied per patient depending on diagnosis and protocol. Patients were seen at least weekly while on treatment for clinical examination.

Data and Analysis

This retrospective review was approved by our institutional review board (IRB). Data were abstracted from each patient's medical records including age at diagnosis and treatment, complete or subtotal resection, any pre-radiation post-operative toxicities, chemotherapy regimen, histology and molecular tumor information, pre-treatment hematologic baseline lab values, and radiation dose. Patient data was reviewed for acute toxicities including gastrointestinal (GI) toxicity (nausea, vomiting, esophagitis, dysphagia, diarrhea), dermatologic toxicity, alopecia, as well as anemia, thrombocytopenia and leukopenia also specifically evaluating lymphopenia and neutropenia. Institutional guidelines dictated that transfusions were given for hemoglobin <9g/dL. All toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Disease-free survival (DFS) was evaluated using Kaplan-Meier survival analysis and log rank testing, toxicity rates were compared using Fisher's exact test. All statistical analyses were conducted using SPSS v.22 (IBM, Armonk, NY, USA). Due to small patient numbers, multivariate analysis was not performed.

RESULTS

A total of 38 patients were treated and available for analysis. Thirteen patients were treated with photon CSI and 25 with VBSpCSI. The median age at diagnosis was 7 years, and the median age at treatment was 7.5 years (range 2-16). Cohorts were well-match with perspective to their gender distribution, age at treatment, and CSI dose (Table 1). Median follow-up time was 20.5 months (range 1 to 100 months) for all analyzed patients but differed between the two groups due to changes in institutional practice after opening of the proton center in 2014. Median follow-up for the VBSpCSI cohort was 13 months (range 2 to 15 months) and median follow-up for the photon cohort was 52 months (range 1 to 100 months), ($p<0.0001$). Regarding systemic therapy, a similar proportion of patients received chemotherapy either before or concurrent with radiotherapy; however, when assessing concurrent chemotherapy alone, a significantly higher proportion of patients on the photon cohort received concurrent chemotherapy (69% vs 32%, $p=0.042$). When excluding patients with nongerminomatous germ cell tumors who do not receive concurrent chemotherapy with radiation, the difference was no longer significant (69% vs 38%, $p=0.16$).

All patients received radiation with a single modality, except for one patient who received 7.2 Gy in 4 fractions using 3DCRT photon CSI due to emergent cord compression, and then transitioned to VBSpCSI for the remainder of the course and was included in the VBSpCSI cohort. The 2-year disease-free survival (DFS) in the two cohorts was 81.3% for VBSpCSI and 61.5% for photon CSI ($p=0.18$).

Prominent acute toxicities are reported in Table 2. Rates of acute Grade 2+ GI toxicity were significantly lower in the VBSpCSI group compared to the photon CSI group (24.0% vs 76.5% p=0.0045). Rates of Grade 2+ nausea were also lower (24.0% vs 61.5% p=0.0353) with VBSpCSI, but there was no significant difference in acute dysphagia (4% vs 7.7% p=1.00). No patient treated with VBSpCSI had any-grade esophagitis, while 38% in the photon cohort had any-grade esophagitis (p=0.0026). One patient in the photon cohort had grade 2 esophagitis.

Detailed serial labs were available for 34 patients, 10 in the photon CSI group and 23 in VBS proton CSI. Acute Grade 2+ hematologic toxicity was present in 100% (10) of the photon cohort and 82% (19) of the VBSpCSI cohort (p=0.2890). Anemia requiring packed red blood cell (pRBC) transfusions occurred at significantly lower rates in patients treated with VBSpCSI (21.7% vs 60.0% p=0.049). There were no grade 5 toxicities of any type and no treatment delays due to acute toxicities.

In the VBSpCSI cohort, rates of leukopenia were 74% Grade 2+ (17/23) and 22% Grade 3+ (5/23). In the photon cohort, rates of leukopenia were 70% Grade 2+ (2/10) and 50% Grade 3+ (5/10). No statistical difference was observed between cohorts for all grade 2+ leukopenia (p=0.696). However, Grade 4+ lymphopenia occurred less in patients treated with VBS proton CSI (33.3% vs 77.8% p=0.0457).

DISCUSSION

Advances in surgery, chemotherapy and CSI have greatly improved outcomes in medulloblastoma with 5 year PFS being reported at rates up to 85%[13,14,18]. Use of proton therapy is increasing and studies comparing proton CSI to photon CSI showing equivalent survival rates with the benefit of decreased toxicity[13,14,19]. Dosimetric studies comparing proton CSI to different photon techniques including 3D conformal radiotherapy (3DCRT), IMRT, VMAT and tomotherapy have highlighted the substantial dose reduction to thoracic and abdominal organs using protons[5-7,9-11]. Multiple model-based studies have extrapolated and attributed the sparing of normal tissue using protons to a reduction in lifetime risk of secondary malignancy, though clinical long-term follow-up data is still maturing[20,21]. When comparing different proton techniques, Giantsoudi et al. showed significant dose sparing to the anterior and vertebral body with VBS plans compared to whole vertebral body treatment, as well as a dramatic reduction in mean dose to the esophagus to less than 1.8 Gy[8]. In our present study, the use of VBSpCSI has led to clinically significant improvements in hematologic and gastrointestinal toxicity without compromising disease-free survival.

Regarding gastrointestinal toxicity, in the VBSpCSI adult population reported by Brown et al. at MD Anderson, rates of Grade 2 nausea were greatly improved with proton CSI versus photons (26% vs 71% for Grade 2, p=0.004)[17]. Our study has replicated similar findings in the pediatric population (24% vs 61% for Grade 2+ nausea/vomiting, p=0.0353). Additionally, the adult comparison yielded significantly improved rates of esophagitis requiring management (5% vs 57%), which is also re-demonstrated in the current study (0% vs 38%, p=0.0026). It should be no

surprise that the rate of acute esophagitis was nil as the esophagus receives <8% of prescription dose in VBSpCSI.

Hematologic toxicity is also a significant issue with CSI as bone marrow is highly radiosensitive, with pediatric patients at higher risk than adults[17,22,23]. In the data reported by Brown et al., photon CSI resulted in significantly higher rates of anemia and dose to the vertebral body correlated significantly with decreasing white blood cell and platelet counts[17]. In the pediatric population reported by Wong from Los Angeles California, 89% of patients treated with photon VMAT CSI had anemia requiring transfusions[24]. Recent multi-institutional data from 97 pediatric patients (abstract form only) showed improved lymphocyte counts and platelets with protons versus protons[25]. Our study corroborates that photon CSI is associated with higher rates of hematologic toxicity (lymphopenia, transfusions), and showed that VBSpCSI yields lower rates of transfusion (21% vs 60%, p=0.049).

The limitations of this study include the relatively small number of patients in each cohort with complete data sets available for review. This prevented a more robust statistical analysis, particularly multivariate analysis. To capture more CSI patient data we also included non-medulloblastoma histologies and these patients were mostly treated with chemotherapy prior to radiation. It should also be noted that the two cohorts were treated in relatively different eras due to completion of the proton center in 2014, and patients received chemotherapy on protocols which were accruing at the time of treatment and were assigned non-randomly to CSI technique. Due to these factors and the lack of multivariate analysis, we cannot fully exclude the possibility of additional statistical interaction between our significant outcomes and the aforementioned differences between cohorts.

Currently, proton CSI has become the preferred modality to spare anterior structures without sacrificing oncologic outcomes. An argument has been made that it should be the standard of care, and this is a view shared by some experts in the field[19]. Our review shows that VBSpCSI delivers less acute toxicity without compromising disease control, which supports its use as the standard of care treatment. Furthermore, improvement in gastrointestinal and hematologic toxicities with VBSpCSI were observed in similar comparisons in the adult setting.

In the current era of treatment for medulloblastoma, required dose to the thecal sac remains 23.4 Gy for standard-risk patients as ACNS 0331 demonstrated the perils of dose de-escalation, at least until further advancements in treatment or patient selection are achieved. Dose-volume reduction is another method of de-escalation in the patient population at the highest risk of late treatment-related morbidity and secondary malignancy. Based on our results, we interpret VBSpCSI as volumetric de-escalation with clinically significant improvements in the acute toxicity profile.

CONCLUSIONS

In our institutional comparison, VBSpCSI was associated with significantly less hematologic and gastrointestinal toxicity than photon CSI. This is a direct clinical realization of the modeled dosimetric benefits of this technique and has become the standard of care at our institution for all patients receiving CSI. Further research is warranted to confirm the favorable long-term spine

outcomes seen in a previous study[15]. We believe that VBSpCSI should be the favored modality for the treatment of tumors requiring CSI.

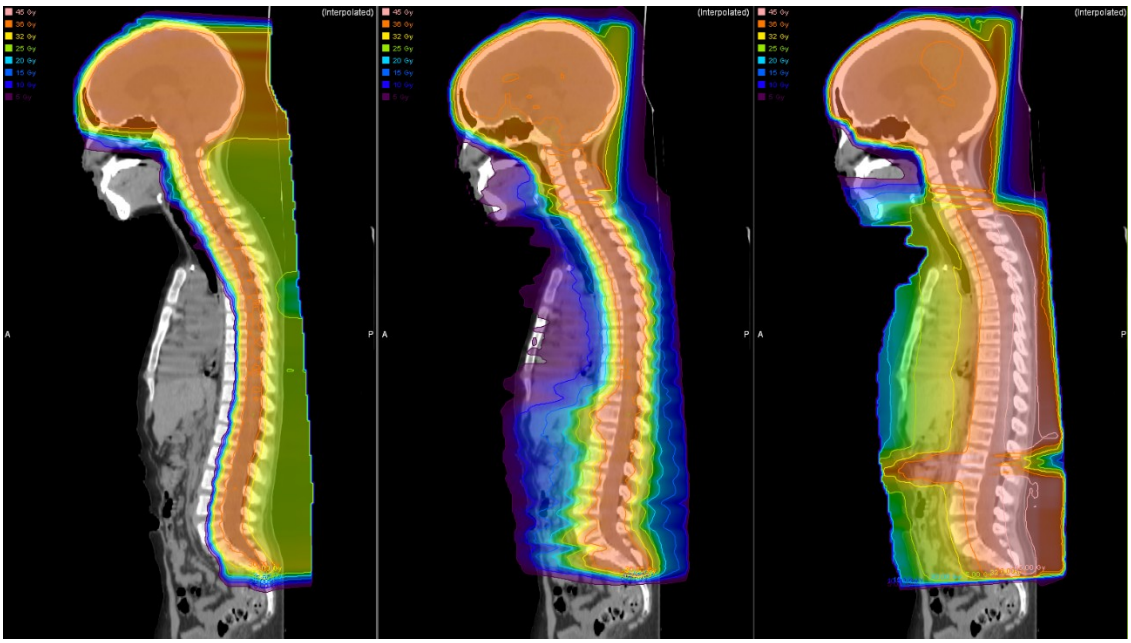
ACKNOWLEDGEMENTS

None

FUNDING

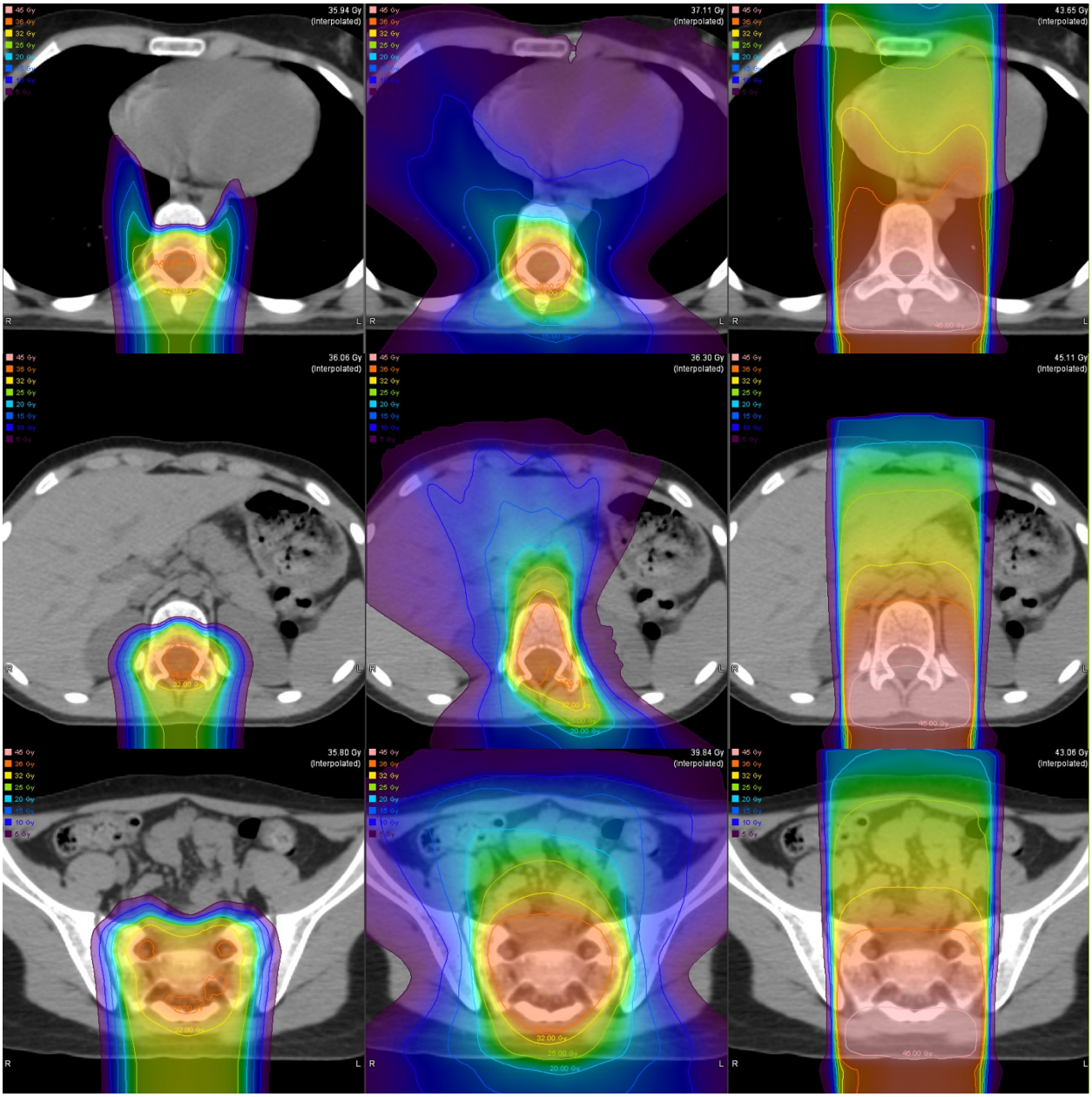
None

Figure 1A: Sagittal Dose Profiles of Craniospinal Irradiation Techniques



Three sample craniospinal plans delivering 36 Gy for an 11 year old boy with a diagnosis of nongerminomatous germ cell tumor. Left (delivered plan): vertebral body sparing proton craniospinal irradiation (VBSpCSI). Middle: volumetric modulated arc therapy (VMAT) with photons. Right: Classical posterior-anterior (PA) photon beams with feathered match lines. Isodose lines are shown at 45 (right only), 36, 32, 25, 20, 15, 10, and 5 Gy.

Figure 1B: Axial Dose Profiles of Craniospinal Irradiation Techniques



Sample radiation dose profiles for VBSpCSI (left), VMAT (middle), and classical PA photons (right) at the level of the thorax (top row), abdomen (middle row), and pelvis (bottom row). Isodose lines are shown at 45 (right only), 36, 32, 25, 20, 15, 10, and 5 Gy.

CONFLICT OF INTEREST STATEMENT

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from **brian.chou001@luhs.org.**

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Proton and Photon Therapy-Induced Hematologic Toxicity in

Medulloblastoma Patients. International Journal of Radiation Oncology Biology Physics 2019;105:E625-E6.

Figure Legends:

Figure 1A: Sagittal Dose Profiles of Craniospinal Irradiation Techniques

Three sample craniospinal plans delivering 36 Gy for an 11 year old boy with a diagnosis of nongerminomatous germ cell tumor. Left (delivered plan): vertebral body sparing proton craniospinal irradiation (VBSpCSI). Middle: volumetric modulated arc therapy (VMAT) with photons. Right: Classical posterior-anterior (PA) photon beams with feathered match lines. Isodose lines are shown at 45 (right only), 36, 32, 25, 20, 15, 10, and 5 Gy.

Figure 1B: Axial Dose Profiles of Craniospinal Irradiation Techniques

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