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## RESEARCH ARTICLE

# A comprehensive review of 30 years of pediatric clinical trial radiotherapy dose constraints

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## Abstract

**Background:** Radiation therapy normal tissue dose constraints are critical when treating pediatric patients. However, there is limited evidence supporting proposed constraints, which has led to variations in constraints over the years. In this study, we identify these variations in dose constraints within pediatric trials both in the United States and in Europe used in the past 30 years.

**Procedure:** All pediatric trials from the Children's Oncology Group website were queried from inception until January 2022 and a sampling of European studies was included. Dose constraints were identified and built into an organ-based interactive web application with filters to display data by organs at risk (OAR), protocol, start date, dose, volume, and fractionation scheme. Dose constraints were evaluated for consistency over time and compared between pediatric US and European trials

**Results:** One hundred five closed trials were included—93 US trials and 12 European trials. Thirty-eight separate OAR were found with high-dose constraint variability. Across all trials, nine organs had greater than 10 different constraints (median 16, range 11–26), including serial organs. When comparing US versus European dose tol-

**Abbreviations:** CCG, Children's Cancer Group; COG, Children's Oncology Group; DCOG, Dutch Childhood Oncology Group;  $D_{max}$ , maximum dose; GPOH, German Society of Pediatric Oncology and Hematology; OAR, organs at risk; PENTEC, Pediatric Normal Tissue Effects in the Clinic; POG, Pediatric Oncology Group; QUANTEC, Quantitative Analyses of Normal Tissue Effects in the Clinic; SRS, radiosurgery; US, United States.

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erances, the United States constraints were higher for seven OAR, lower for one, and identical for five. No OAR had constraints change systematically over the last 30 years.

**Conclusion:** Review of pediatric dose-volume constraints in clinical trials showed substantial variability for all OAR. Continued efforts focused on standardization of OAR dose constraints and risk profiles are essential to increase consistency of protocol outcomes and ultimately to reduce radiation toxicities in the pediatric population.

#### KEYWORDS

constraints, oncology, pediatric, radiotherapy

## 1 | INTRODUCTION

Survival rates in pediatric cancers continue to improve, with 5-year survival rates ranging from 68% to 86%.<sup>1</sup> However, a consequence of improving survival outcomes is the increased long-term morbidity of treatment toxicities.<sup>2–4</sup> Radiation therapy is necessary for childhood cancer types and has evolved with the growing awareness of long-term sequelae following treatment.<sup>5</sup> This is of particular concern among children and adolescents for whom irradiation of actively developing tissues impairs growth and maturation. Accordingly, radiation exposure can cause neurocognitive growth, and reproductive deficits, as well as organ dysfunction and risk of subsequent malignancies.<sup>6–12</sup> Modern radiation techniques, with improved imaging modalities, comprise one such effort to reduce late adverse effects. While these advanced techniques deliver highly uniform and conformal dose distributions to the target volumes, incidental irradiation of surrounding normal tissues, referred to as organs at risk (OAR), are more variable and depend on their proximity to the target volume, the prescribed tumor dose, the radiation technique, and the permitted dose-volume constraints used during treatment planning.<sup>13</sup>

Evidence-based dose-volume risk guidelines and consensus constraints are essential to provide optimal tumor control in a safe and effective manner that minimizes toxicity. Clinical trials requiring radiotherapy rely on the current state of knowledge about normal organ dose-response to inform the choice of dose constraints in protocols. However, organ-specific constraints specified in adult protocols have been shown to be highly variable.<sup>14</sup> To counter this, task forces have formed to evaluate normal tissue tolerances and propose corresponding dose-volume constraints, with notable collaborations being Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) and Pediatric Normal Tissue Effects in the Clinic (PENTEC) in adults and children, respectively.<sup>13,15</sup> This study provides a comprehensive review of the dose-volume constraints from closed clinical trials in the Children's Oncology Group (COG) as well as others outside of the United States, in an effort to describe the heterogeneity in OAR-specific dose constraints in contemporary and historic protocols. Such variations undermine the clinical trial paradigm of consistency and motivate an organized effort to redefine and standardize OAR dose constraints across clinical trials. To our knowledge, an evaluation of dose constraint variability for pediatric trials has not been previously documented.

## 2 | METHODS AND MATERIALS

All closed pediatric trials from the COG website (which also includes the Pediatric Oncology Group [POG] and the Children's Cancer Group [CCG]) were queried from inception until January 2022 (a 30-year period) and included if radiation was used. A sampling of European studies was included, based on all international protocols actively recruiting patients from 2016 to 2017 in the Netherlands. The European trials comprised the International Society of Pediatric Oncology (SIOP), European and American Osteosarcoma Studies (EURAMOS), German Society of Pediatric Oncology and Hematology (GPOH), Dutch Childhood Oncology Group (DCOG), EWING2008, and European Paediatric Soft tissue sarcoma Study Group (EpSSG). Trial OAR dose constraints were reviewed, including both conventionally fractionated constraints with photons or protons, and radiosurgery (SRS) constraints.

Dose constraints were compared in three ways. First, graphical scatter plot overviews of all values were created for each organ to facilitate an overall comparison of heterogeneity. Second, for a more quantitative comparison of high-dose constraints between pediatric US and European groups,  $D_{\max}$  (maximum dose) or the dose to a volume greater than or equal to 20% was compared. Third, specific commonly used OAR were investigated for variability in the volume percent constraints. OAR constraint data were visualized by building an interactive web application. This website application renders OAR constraint data in both plot and table format based on the pediatric group, protocol, date enrollment started, dose, volume, and number of trials with the same constraint. Users may apply filters to display associated data.

## 3 | RESULTS

One hundred five trials were included: 93 from the COG website (COG/CCG/POG) and 12 protocols recruiting patients in European countries—10 from European collaborative groups and two from national groups (DCOG in the Netherlands and GPOH in Germany). The trials included are listed in Table S5. Most of the protocols involved concurrent chemoradiation with chemotherapeutic agents, including vincristine, cisplatin, carboplatin, cyclophosphamide, ifosfamide, and

**TABLE 1** Common dose-volume values for organs at risk.

Organ	Dose	Volume metric (%)
Bladder	V45–V50	50–100
Brain	V50–V60	0–45
Cochlea	V30–V40	50–100
Heart	V30	40–100
Kidneys	V12	20–100
Kidneys	V14.4	33–100
Kidneys	V20	33–50
Lungs	V15	33–100
Lungs	V20	20–35
Liver	V20	33–100
Parotid	V26–V30	50
Retina	V45	1–100
Small/large bowel	V45	20–75

etoposide. Anthracyclines were frequently used but generally not during the radiation therapy course.

Thirty-eight unique OAR were found. The number of different constraints per OAR within the protocols varied widely, ranging from a single constraint for the hypothalamus from COG ACNS 0222 to 29 unique kidney constraints within 68 protocols. Other OAR with at least 10 unique constraints included the liver, lungs, spinal cord, optic chiasm, optic nerves, heart, brainstem, and brain at 26, 24, 20, 16, 14, 13, 11, and 11, respectively. An example of the variability of dose constraints in a critical organ can be seen with the spinal cord constraints ranging from a  $D_{\max}$  of 40 Gy up to V57 Gy less than 10% (less than 10% of the volume receiving 57 Gy). For several OAR, different protocols chose the same dose metric but assigned a wide range of volumetric limits. For example, the heart V30 Gy limit ranged from 40% to 100%. For kidney, V12 Gy was limited by some protocols to 20% but for others, up to 100% and the V14.4 Gy limit ranged from 33% to 100%. For kidney D50%, constraints ranged from 8 to 24 Gy. For cochlea, the allowed dose for 50% volume ranged from 20 to 40 Gy. Further dose-volume metrics are listed in Table 1. Example diagrams illustrating the range of constraints, pediatric group, and number of trials associated with each constraint can be seen in Figure 1A–C.

When comparing the high dose-volume constraints ( $D_{\max}$  or dose to a volume  $\leq 20\%$ ) between pediatric US constraints and European constraints, 13 of the 38 OAR had at least two constraints with either a  $D_{\max}$  or a volumetric parameter of 20% or above. US and European constraints matched in five of these OAR (brain, cornea-lacrimal gland, optic chiasm/nerves, and small-large bowel). European constraints had higher dose allowances in one OAR (brainstem), while US constraints were higher in seven OAR (spinal cord, bladder, heart, kidneys, lungs, liver, and mandible) (Table 2).

The conventionally fractionated constraints for all trials organized by the OAR are listed in Table S1, with available PENTEC data

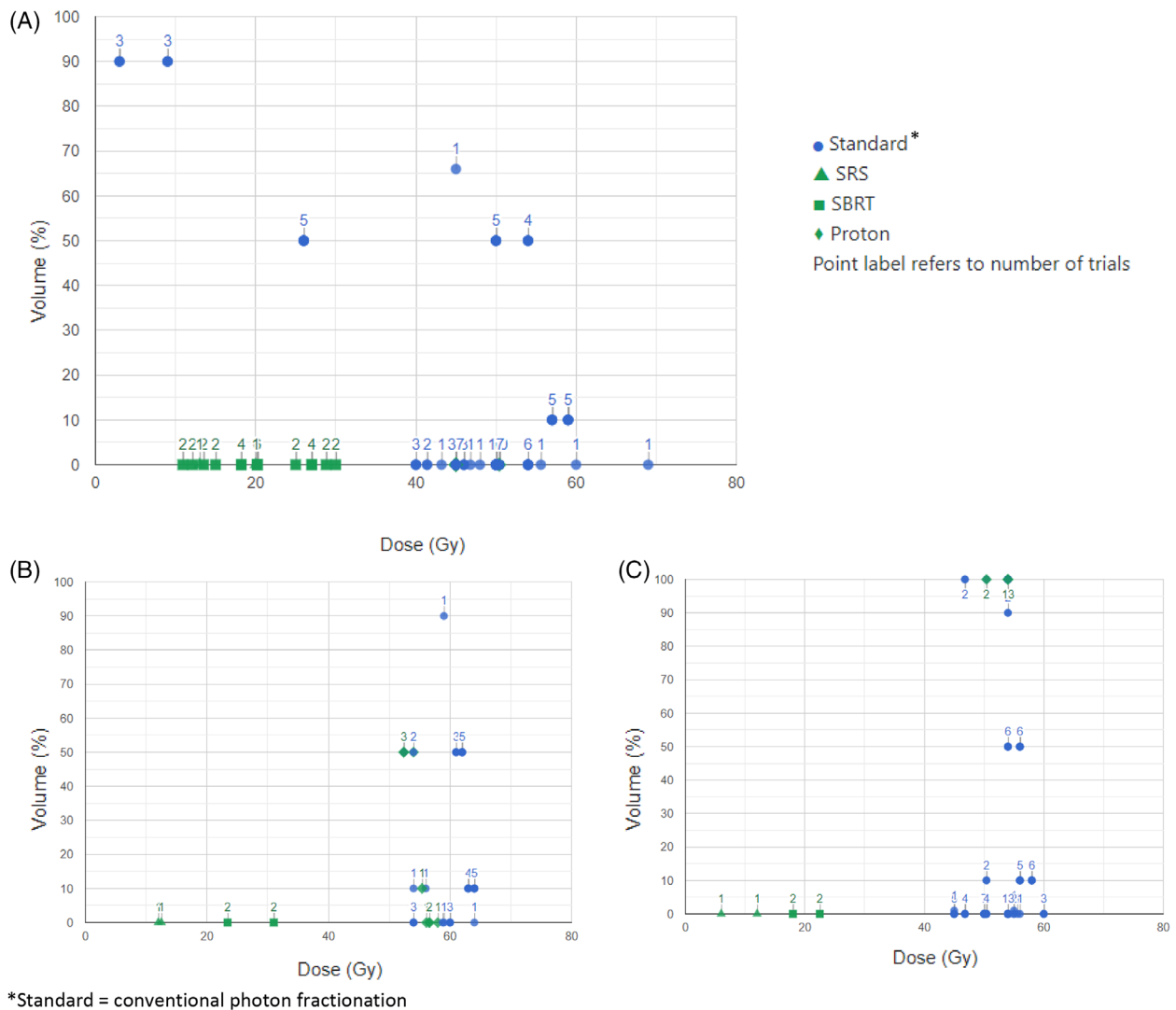
listed for comparison.<sup>15–19</sup> PENTEC is an ongoing systematic effort to summarize and, where feasible, suggest OAR-based constraints for children and adolescents based on published evidence.<sup>15</sup> Four protocols addressed proton constraints (additional three trials that are currently active were not included) and three trials included SRS constraints (additional two trials currently active were not included) listed in Tables S2 and S3. Additionally, the interactive web application URL is also available in Supporting Information Data S4. To account for changes in constraints over time, we included within the web application the option to filter by start date of the protocol. Although much has changed technologically over the past 30 years, radiotherapy dose constraints generally did not show any consistent pattern of change over time for any of the OAR including the spinal cord, brainstem, optic apparatus, lungs, heart, and kidneys.

## 4 | DISCUSSION

In our review of 105 pediatric trials, there was substantial variability in recommended dose-volume constraints among all OAR. While heterogeneity is present in adult clinical trials, many protocols refer to pre-existing OAR guidelines from QUANTEC, the American Association of Physicists in Medicine Task Group (AAPM-TG) 101, and Hypofractionated Treatment Effects in the Clinic (HyTEC).<sup>13,20,21</sup> A comparable pediatric consensus guideline was not previously available, although it is well known that late effects in normal tissues vary across the age spectrum and can lead to devastating consequences.<sup>6</sup> It is reassuring that the current PENTEC guidelines are now being developed and will help promote more consistency among recommended dose constraints across protocols.

To a certain extent, the degree of variability can be justified by different treatment goals for various cancer histopathologies, target volumes, sex, age, and the use of concomitant treatments. That is, the accepted normal tissue risk tolerance for some diagnoses might be greater if their curability is less likely. Nevertheless, consistency in constraints was poor even for the same diagnosis, chance for survival, or similar exposures to chemotherapy. For serial structures such as the spinal cord, optic chiasm, and optic nerves, reduced variability between dose constraints would be expected for a  $D_{\max}$  constraint compared to volumetric constraints. However, this was not seen with 20, 16, and 14 unique constraints across the trials for these three structures, respectively. When comparing pediatric US constraints to European constraints, constraint tolerances were higher for parallel organs, including the bladder, heart, lungs, liver, and kidneys. For serial structures, dose tolerances were mixed with the COG protocols allowing for a higher dose for the spinal cord, but a lower dose for the brainstem.

One might expect dose constraints to change over time, consistent with new normal organ dose-response data becoming available. However, none of the OAR had a systematic pattern of change in protocol dose constraint values over time to indicate an increase or decrease in the tolerated dose. Rather, the variations were either in choice of the dose-volume pairing or nonsystematic changes, neither of which



**FIGURE 1** Representative plots of the (A) spinal cord, (B) brainstem, and (C) optic chiasm constraints based on the number of trials and treatment modality.

indicated the influence of new information but are more likely due to a lack of both good dose-response data and consensus by protocol committee members. Additionally, review of the currently active protocols also shows constraints were consistent with previous trials with no consistent pattern of change. This finding further highlights the need for more evidence-based, consistent constraints across protocols.

It is provocative to speculate on the reasons for the observed heterogeneity in constraints across protocols or even continents. Presumably, the scientific investigations used to derive constraints are available to clinicians internationally. In addition, we would not expect any cultural differences in the degree of tolerance for adverse outcomes. It would be interesting to collate dose constraints from other continents and compare these with the US and European values identified. It would be even more nuanced to compare constraints within specific countries in these continents. To date, none of the cited constraints were derived from a stringent formal process as is customary in clinical guideline development, which likely contributed to

the observed heterogeneity. This observation was mirrored in the setting of recommendations for risk-based surveillance among childhood cancer survivors, for which substantial international variation was demonstrated, and acted upon, with the inception of the International Guideline Harmonization Group (IGHG).<sup>22</sup> Additionally, consensus is lacking for dose-volume constraints for protons and SRS with mentions of these constraints in seven and five trials, respectively, including currently active trails. We encourage the PENTEC task group and future task groups to evaluate both modalities, as there is little consensus on proton constraints, and also an increasing number of trials using SRS and stereotactic body radiotherapy (SBRT) to ablate metastatic disease.

Recently, five PENTEC reviews have been published on the rates of neurocognitive effects and brain necrosis, breast hypoplasia and impaired lactation, primary hypothyroidism, pulmonary injury, and salivary and dental complications for childhood cancer survivors treated with radiotherapy.<sup>16,17,19,23,24</sup> The model for a 5% risk of

**TABLE 2** High dose-volume constraints: A systematic comparison of US and European pediatric cancer treatment protocols.

	US pediatric constraints		European pediatric constraints		Higher tolerance dose
	$D_{\max}$	Volumetric constraint	$D_{\max}$	Volumetric constraint	
Bladder		V70 < 20%	<60		US
Brain	<60		<60		Equal
Brainstem		V63 < 10%		V64 < 10%	Europe
Cornea-lacrimal	<41.4		<41.4		Equal
Heart	<50		<30.6		US
Kidneys	<20		<19.8		US
Lungs		V20 < 20%	<18		US
Liver	<50		<23.4		US
Mandible		V77 < 1cc	<60		US
Optic chiasm	<60		<60		Equal
Optic nerves	<60		<60		Equal
Bowel	<50		<50		Equal
Spinal cord		V57 < 10%	<54		US

Abbreviations:  $D_{\max}$ , maximum dose; US, United States.

subsequent IQ < 85 suggested constraints stricter than the current pediatric protocols, while the  $D_{\max}$  constraints related to necrosis were similar in these protocols to the recommended PENTEC constraints (Table S1).<sup>18</sup> The PENTEC dose-toxicity data regarding salivary function demonstrated a 13%–32% risk of acute and chronic grade 2 xerostomia, with a mean parotid dose of 35–40 Gy.<sup>19</sup> Within our review of current and active trials, parotid constraints were more restricted ranging from V20 < 25% to V34 < 50%, and a solitary  $D_{\max}$  constraint of 40 Gy. Breast and thyroid constraints were not presented in our reviewed protocols for comparison with the PENTEC data, and additional OAR publications are highly anticipated.

To our knowledge, this is the first study to provide a comprehensive review of radiotherapy dose constraints within a broad range of pediatric clinical trials. Our intentions were to describe the current landscape of OAR-specific dose constraints, display a comprehensive guide and interactive website for pediatric constraints used on trials, and present the high variability and inconsistencies within these trials to continue to promote the interest and support for task groups to establish quantitative, evidence-based dose-volume risk guidelines for radiation therapy in childhood cancers.

## 5 | CONCLUSION

Review of pediatric dose-volume constraints in clinical trials showed substantial variability for all OAR, both for US trials and for European relative to US trials. None of the OAR had constraints systematically change over time, indicating that the variations seen were not due to the application of new dose-response information, but more likely due to a lack of both robust dose-response data and consensus by protocol committee members who establish the constraints. Contin-

ued efforts focused on standardization of OAR dose constraints and risk profiles are essential to increase consistency of protocol outcomes and ultimately to reduce radiation toxicities in the pediatric population.

## CONFLICT OF INTEREST STATEMENT

Cecile Ronckers has a Dutch Cancer Society Grant for Jr Group Leaders (grant #UVA2012-5517, 2013-2018). Marjorie Jones contributed to this research project within the USC/CHLA Summer Oncology Research Fellowship Program, supported by a National Cancer Institute R25 grant CA225513, the Norris Comprehensive Cancer Center, Children's Hospital Los Angeles, Concern Foundation for Cancer Research, and Tri Delta. Louis S. Constine has grants/contracts from the University of Alabama for COG Survivorship Guidelines, has royalties/licenses with Up-to-date, Springer, and Wolters Kluwer, has honoraria for the American Society for Hematology and the University of Miami Radiation Oncology Grand Rounds, and participates on the Pediatric Oncology Board. The remaining authors have no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Supporting Information of this article.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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