Childhood Cancer Survivor Study - Analysis Concept Proposal for Consideration from the Epidemiology/Biostatistics Working Group

Title: Dosimetric Uncertainty in Radiation Dose Reconstruction Method used for CCSS

Working Group and Investigators: Epidemiology/Biostatistics

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Background and Rationale:

For CCSS studies, organ doses for individual patients are universally determined based on retrospective dose reconstructions. For each patient, the medical record is reviewed for details of the radiation therapy (RT), including age at time of treatment, treatment site, prescribed and delivered dose, beam arrangement, beam energy, field size, treatment depth, and field blocking. These details are then used to reconstruct the treatments using a library of average-size-for-age (infant through adult) generic phantoms (Figure 1) and analytical calculation models (Stovall et al. 2006; NCRP 2011). The phantoms were modeled using published data for the size and stature of infants, children, and adolescents (Snyder et al. 1977).

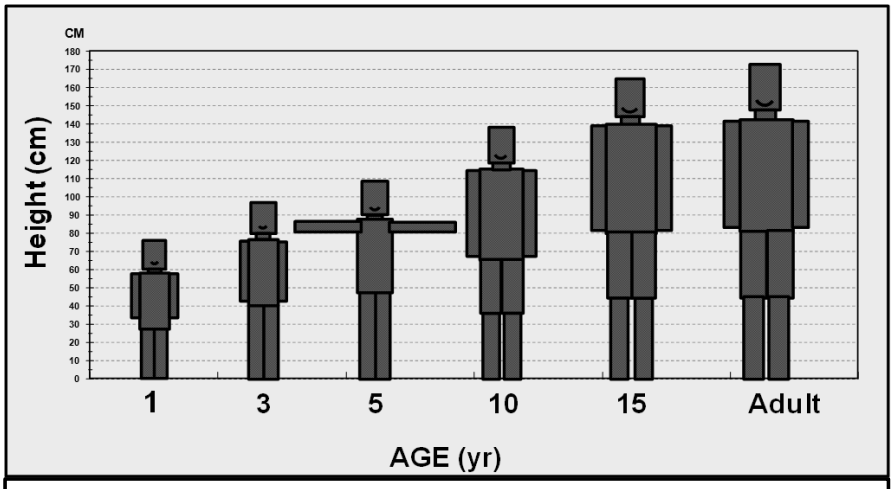

Figure 1: Library of average-size-for-age (infant through adult) generic block-shaper water phantoms models used to reconstruct the treatments for patients in CCSS.

Dose reconstructions using generic phantoms are necessary because most patients in CCSS were treated with conventional RT before computed tomography (CT) was used for treatment planning. As such, doses to non-target organs, and even positions of those organs, are not available. Even in the CT treatment planning era scans include only anatomy near the treatment location.

Given the lack of information on non-target organ doses and locations, the approach of performing calculations in generic phantoms is reasonable and necessary. However, this approach results in some uncertainty in

reconstructed dose. A notable source of uncertainty arises from calculating dose in a generic (block-shape) water phantom rather than in a patient/phantom with heterogeneous tissue composition and irregular (non-block) body dimensions. This source of uncertainty, hereafter referred to as "generalized phantom uncertainty", will be quantified in Specific Aim 1 of the proposed project. Another important source of uncertainty in reconstructed doses arises from lack of information regarding position of organs in a patient; for each reconstruction a survivor is assigned to a generic phantom for calculations. This assignment is based on age at time of RT. Organs within each age phantom are at predefined positions. This second source of uncertainty, hereafter referred to as "organ position uncertainty", is more difficult to quantify. In Specific Aim 2 of the proposed project, we will examine the possible magnitude of organ position uncertainty for a sample population of patients. Data from Specific Aim 2 could be used to determine if a larger investigation is warranted. Both generalized phantom and organ position uncertainties are highly dependent on distance from the field edge because dose decreases very rapidly as distance from the field increases. Additionally, magnitude of the out-of-field dose is also greatly influenced by field size, i.e., lower for smaller fields.

Specific Aims and Objective

The objective of this project is to better understand uncertainty in the radiation dose reconstruction method used for CCSS that arises from (1) calculating dose in a generic (block-shape) water phantom rather than in a heterogeneous irregularly shaped patient/phantom and (2) lack of knowledge of the true position of a patient's organs with respect to the position of the organs in the generic phantom used for dose reconstruction. *Both aims will be carried-out for whole brain and posterior fossa RT:*

- Specific Aim 1: Quantify the difference between known doses in an anthropomorphic phantom and doses that are reconstructed in a generic (block-shape) water phantom.

- Specific Aim 2: For a sample population of patients, examine the range and magnitude of difference between organ doses that are calculated when the organ position is precisely known (defined using whole body-CT scan) and when the organ position is only approximated (defined within generic phantom used in CCSS dose reconstructions).

In this study, we are focusing on brain RT, because in the expanded CCSS cohort (the study population: see below), brain RT was conducted in a similar manner across the CCSS institutions; these generally fell into two categories, whole brain and posterior fossa boost, large and small fields, respectively.

Analysis Framework:

Study Population: All survivors of the expanded cohort of CCSS who had RT will be included. Specifically, we will query the RT records database for survivors treated with whole brain and posterior fossa boost RT. For the identified records, we will obtain the treatment field data, e.g., energy, field size, and field placement. Then, we will design whole brain and posterior fossa treatment plans for Specific Aims 1 and 2 based on the field data from the queried records to replicate the treatment received by these survivors.

The outcomes of interest, exploratory variables, and examples of tables/figures are described separately for Specific Aim 1 and Specific Aim 2 below.

Outcome of Interest Specific Aim 1: Difference between known doses and reconstructed doses to precisely identified points within and outside of the treatment field.

Known doses will be determined using the ATOM anthropomorphic phantom (CIRS Tissue Simulation and Phantom Technology, Norfork, Va), see Figure 2. The height, weight, dimensions, and tissue compositions, are based on guidelines from the International Commission on Radiation Units and Measurements (ICRU). Radiation attenuation within the phantom materials, i.e., soft tissue, average bone tissue, cartilage, spinal cord, spinal disks, lung, brain and sinus are within 1-3% of attenuation within an actual patient. Reconstructed doses will be determined in an generic block-type water phantom (Figure 3) by following the methods used throughout CCSS, We will compare these doses with known doses.

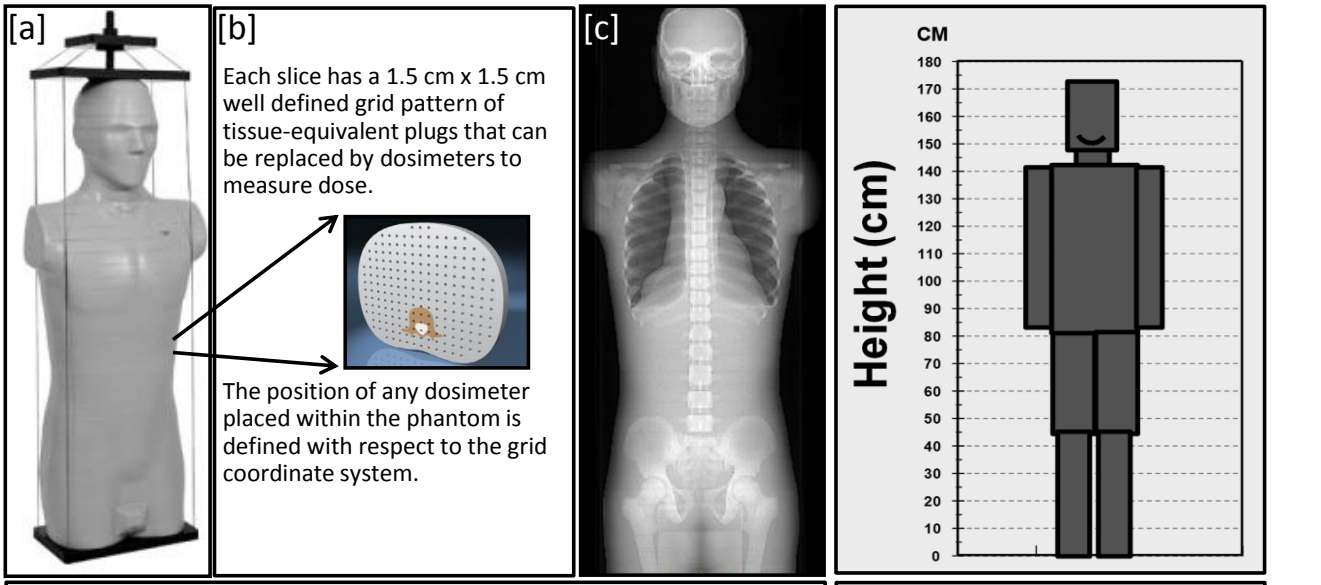

Figure 2: The anthropomorphic phantom that will be used in specific aim 1; composition is tissue equivalent. [a] Photograph of entire phantom. [b] Photograph of an axial slice of the phantom (2.5 cm thickness) showing grid of locations where dosimeters can be positioned. [c] Radiographic image showing anatomic detail within the phantom.

Figure 3: Generic water (block-shape) phantom that will be used for specific aim 1. Phantom shown here is same age and height as the anthropomorphic phantom (Figure 2).

Know Doses: Using the commercially available Eclipse (Varian Medical Systems, Palo Alto, CA) treatment planning system (TPS), we will create two RT treatment plans for a CT scan of an anthropomorphic phantom. **The plans will be based on field data (including energy treatment borders and dose) from the queried records.** The treatment plans will be designed to be representative of typical whole brain and posterior fossa treatment plans for patients in the CCSS expanded cohort. Various points of interest will be defined within and outside of the treatment fields for the two plans. An example is shown in Figure 4, frontal plane view of CT scan of anthropomorphic phantom with whole brain RT treatment plan. The figure illustrates how known dose locations can be specified with respect to field edge (50% dose line): in-field points (A-D) and out-of-field points (10-35).

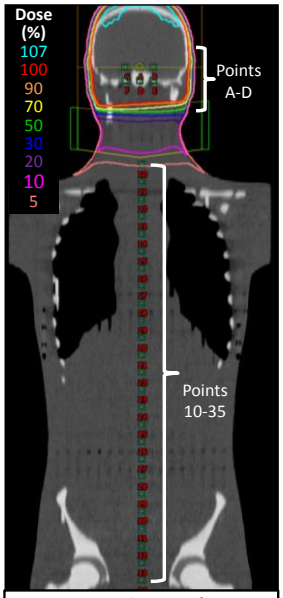

Figure 4: Frontal image of CT scan

The TPS accurately calculates dose within the treatment field. Thus, analysis tools within the TPS software will be used to determine dose to points within the treatment field. Because the TPS does not accurately calculate dose outside the treatment field (Scarboro et al. 2010; Huang et al. 2013), measurements will be performed to accurately determine doses to these locations. Each plan will be delivered to the anthropomorphic phantom and doses will be measured at specified locations throughout the phantom (Figure 5). Dose will be measured using thermoluminescent dosimeters (TLD) which have an accuracy of ± 3% (Kirby *et al.* 2005).

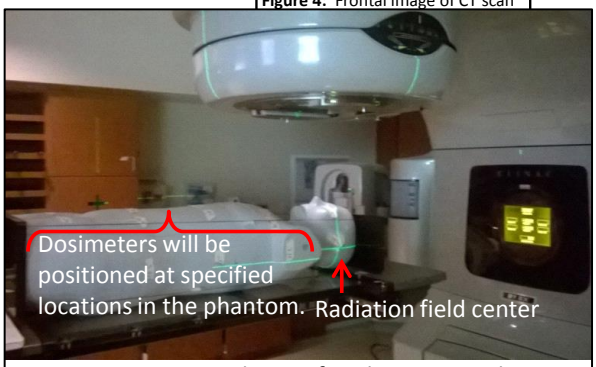

Figure 5: Experimental setup for phantom irradiation.

Reconstructed Doses: The two treatment plans for the anthropomorphic phantom (Figure 2) will each be coded using the current CCSS abstraction methods. For an age appropriate generic phantom, we will calculate the doses to points within the generic water phantom (Figure 3) that correspond to the known dose point locations in the anthropomorphic phantom.

Exploratory Variables Specific Aim 1: The primary variable being explored is field size, i.e., we are assessing calculated dose uncertainty for two treatment field types, large and small.

Examples of Tables/Figures for Specific Aim 1 Results:

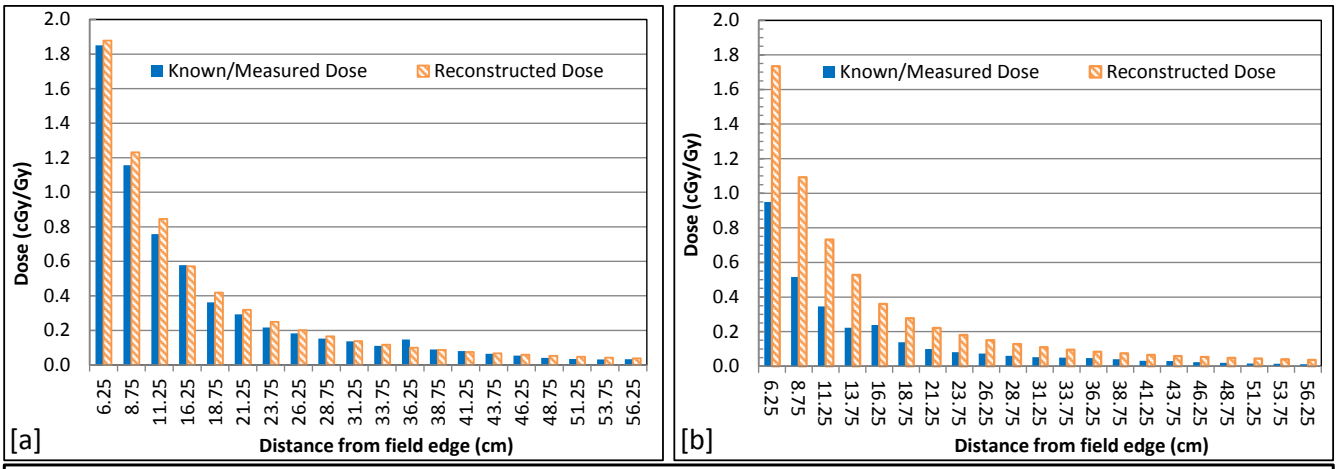

Figure 6: Example figures to compare known/measured dose in the anthropomorphic to reconstructed dose in generic water phantom as a function of distance from field edge phantom; [a] Example of figure if difference is small in magnitude. [b] Example of figure if difference is large in magnitude.

Table 1: Example of how data for this Specific Aim may be presented

	Small Field			Large Field		
Location	**Known dose (Gy)**	**Reconstructed Dose (Gy)**	**Difference as % of known dose**	**Known dose (Gy)**	**Reconstructed Dose (Gy)**	**Difference as % of known dose**
1						
2						
3						
n						

Statistical Analysis for Specific Aim 1: We will use the known/measured dose as a fixed, explanatory variable and assess the uncertainty in the corresponding reconstructed dose given the known/measured dose. The analytic methods we will use include graphical/tabular descriptions such as Figure 6 (or its scatter plot version with lowess smoother) and Table 1, and linear regressions with bias (and potentially variance, too) of the reconstructed doses modeled according to the known/measured dose.

Outcome of Interest Specific Aim 2: Quantify the typical, and extreme, disagreement in organ doses between organ doses that are calculated based on precisely known organ positions (defined using whole body-CT scan) and when the organ positions are only approximated (defined within the generic phantom as CCSS).

Complete anatomical information is required to carry out Specific Aim 2. This information is not available for actual CCSS survivors. Therefore, we will use CT data for 18 pediatric and adolescent patients who underwent craniospinal radiation therapy at MD Anderson Cancer Center (our institution). Because their entire brains and spinal axes were irradiated, their CT scans span from the top of head to mid-thigh (the necessary anatomical data for this aim). The population includes patients ranging from 2 years to 16 years of age (additional descriptive details are provided in special considerations section). This age range of this sample population corresponds to the age range of the generic phantoms used in dose reconstructions for CCSS. For each of the 18 patients, we will create two treatment plans, whole brain and posterior fossa treatments. **As in Specific Aim 1, treatment plans for this sample population will be designed using treatment field information from a record query of patients**

in the expanded CCSS cohort. For the large whole brain fields, comparisons will be done for three organs, the pituitary gland (in-field), thyroid (near-field), and breasts (out-of field). For the small posterior fossa fields comparisons will be done for two organs thyroid (near-field) and breasts (out-of field).

The methodology for Specific Aim 2 is illustrated in Figure 7 and summarized in the following subsections.

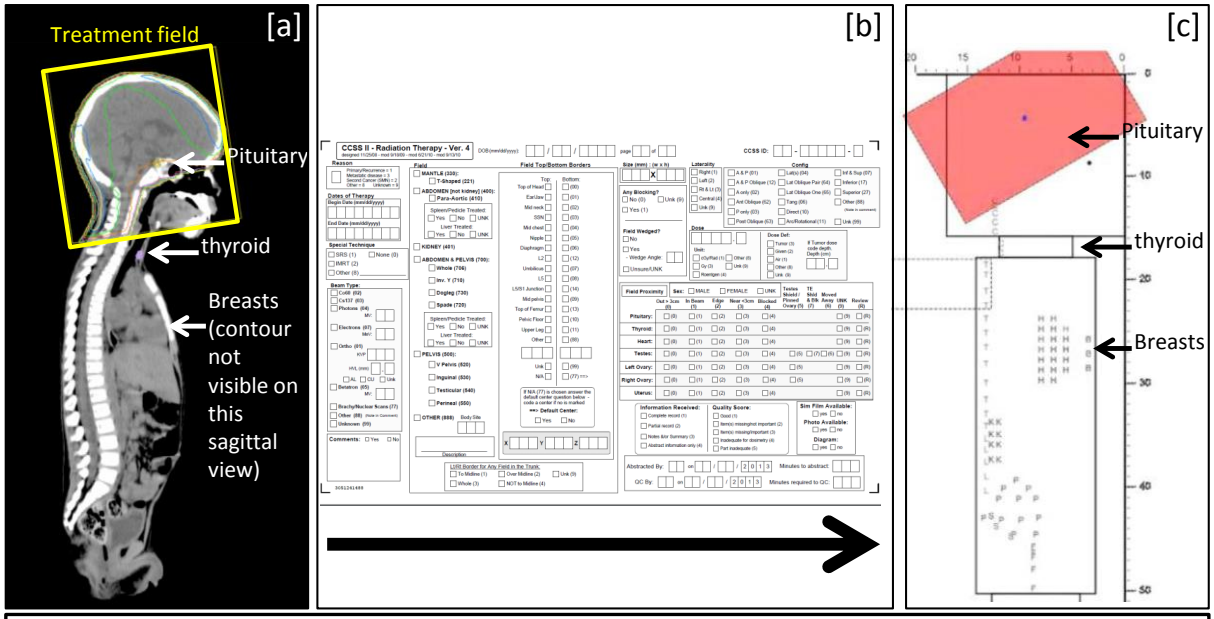

Figure 7: Illustration of method that will be used in Specific Aim 2 (example case) to examine the difference between organ doses that are calculated when an organ position is precisely known (defined using whole body-CT scan) and when the organ position is only approximated (defined within generic phantom). [a] Sagittal view of CT scan for 2-year old patient with "CCSS style" whole brain treatment fields. [b] RT coding sheet that is used for CCSS and that will be used to abstract treatment plans for the sample population (as shown in [a]). [c] Sagittal view of whole brain RT treatment filed positioned on generic (block-style) water phantom sized for age 2 at RT.

Organ doses calculated based on known organ position (defined using whole body-CT scan): Using the commercially available Eclipse (Varian Medical Systems, Palo Alto, CA) treatment planning system (TPS), we will create posterior fossa and whole brain treatment plans (as discussed above) for a CT scans of each of the 18 patients whose ages correspond to the age range of the generic phantoms used for dose reconstructions for CCSS. As described above, **the plans will be based on most common field data (energy treatment borders, dose, etc.) from CCSS records.**

For the pituitary gland, analysis tools within the TPS software will be used to determine the mean dose and dose to points at the center and superior and inferior aspects of the in-field organ. As previously described dose outside the treatment filed is not accurately calculated by TPS software. Thus, dose to the thyroid gland and breasts will be determined based on measured anthropomorphic phantom data. Specifically, for each patient's CT (and for each of the two plans), the distance from the field edge to the center and superior and inferior aspects of both organs will be measured. The dose to each of the points within the organs will then be calculated using analytical models based on measured data (dose as a function of distance from the field edge).

Organ doses calculated based on approximated organ position (defined within generic phantom): For each of the 18 patients, the two treatment plans will be coded using the current CCSS abstraction methods. Treatment fields will be placed using typical default field positions for whole brain and posterior fossa fields. No modifications will be made to standard coding methods. For each patient, calculations will be done for a generic phantom of the appropriate age at time of RT and doses calculated for pituitary, thyroid gland, and breasts.

Exploratory Variables for Specific Aim 2

Patient height: In this component of the study, for each of the 18 patients we will perform an additional reconstruction, for a phantom that is matched to the patients true height (rather than age). Patient heights will be determined from the CT scans. We will compare organ doses reconstructed in this manner to those with standard reconstruction based on age-matched phantom.

Field placement: In this component of the study, for each of the 18 patients we will perform an additional reconstruction, with field positions adjusted such that the inferior treatment field border matches the exact position (with respect to vertebral bodies). Exact field placement will be determined from the CT based plan. We will compare organ doses reconstructed in this manner to those with standard reconstruction based on default field placement.

Examples of Table for Specific Aim 1: A similar table will be generated for each of the 3 organs and for the large and small field sizes. Descriptive statistics will be calculated, e.g., maximum difference, mean standard deviation, etc. These data could also be plotted in figures similar to those shown for Specific Aim 1.

Patient Index	Dose (Gy) from known position defined with CT scan	Reconstructed Dose (Gy) from approximated position within generic phantom			
		No modifications	Field placement Adjusted	Phantom selected to match patient actual height	Field position and phantom height adjusted
1					
2					
.					
18					

Statistical Analysis for Specific Aim 2: The statistical analyses for Specific Aim 2 will descriptive only given small the number of patients.

Special Consideration for Specific Aim 2:

The inclusion criteria for this sample population were that the patients be between 2 and 18 years old at the time of treatment and were treated with craniospinal at our institution between 2007 and 2009. The patients in this study had a mean age of 9.5 years (range, 2-16 years). Patient age, sex, height, weight and BMI are listed in the table below.

Index	Age	Sex	Height (cm)	Weight (kg)	BMI (kg/m^2)
1	2	female	85.0	11.9	16.5
2	4	female	111.7	20.5	16.4
3	6	female	115.2	26.9	20.3
4	8	female	142.0	37.5	18.6
5	10	female	130.6	24.2	14.2
6	2	male	109.2	18.9	15.8
7	4	male	128.0	31.3	19.1
8	6	male	144.8	24.9	11.9
9	8	male	123.4	20.3	13.3

10	10	male	133.0	28.2	15.9
11	12	female	146.0	28.9	13.6
12	13	female	------*data not available------		
13	16	female	162.0	62.0	23.6
14	12	male	166.3	66.5	24.0
15	13	male	173.0	57.5	19.2
16	14	male	162.5	58.6	22.2
17	15	male	172.1	73.3	24.7
18	16	male	191.0	138.2	37.9

*Data were not available in patient's electronic medical record. However, height at time of RT can be determined from CT scan data.