1. Study Title: Comparison of radiation dose reconstruction methods for subsequent neoplasm studies

2. Working Group and Investigators:
Working Groups: Epidemiology & Biostatistics (primary), Second Neoplasms (secondary)

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3. Background and Rationale:

Survival rates following childhood cancer diagnosis have improved dramatically over recent decades due to improvements in treatment.[1] However, long-term survivors of childhood cancer are at risk for a range of late adverse effects of treatment. In particular, radiotherapy substantially increases risk of subsequent neoplasms, which are a leading cause of morbidity and mortality among childhood cancer survivors.[2-5]

Much of our understanding of the relation between radiotherapy and risk of subsequent neoplasms derives from case-control studies of cancer survivors (as reviewed recently[6]), comparing detailed treatment exposure histories among patients who developed subsequent neoplasms to those of patients with a first primary malignancy only. The gold standard measurement of incidental ionizing radiation exposure during radiotherapy involves reconstructing radiation dose to the specific location of

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the subsequent neoplasm (and corresponding location in matched controls), based on individual-level treatment parameters such as patient-specific field configurations and blocking. However, the conduct of such detailed dose reconstruction for each tumor location for a large number of patients such as a full cohort of cancer survivors is resource intensive.

For patients in the Childhood Cancer Survivor Study (CCSS), the MD Anderson dosimetry team has developed a simplified approach to radiation dose reconstruction that is based on the maximum treatment dose each patient has received to particular body regions, including the brain (divided into four segments), pituitary, other head, neck, thyroid, chest, breast (four quadrants for patients who received a mantle field treatment), abdomen, kidney, pelvis, whole spine, arms, and legs, including all treatments within five years of first primary childhood cancer diagnosis (Figures 1-2). The dose to each region includes only the direct in-beam contributions to that region; scatter contribution(s) from other beams outside the region are not included. Doses to each body region have been estimated for the full CCSS cohort and may be utilized for a range of scientific applications, such as estimating the radiation-related risk of developing subsequent neoplasms or other adverse outcomes, investigating joint effects of radiation and genetic susceptibility on risk of adverse outcomes, and risk projection.

In light of the potential widespread utility of this simplified, region-based radiation dose reconstruction approach, we propose to compare the new approach to the gold standard measurement of ionizing radiation exposure to specific tumor locations. Data for the comparison are derived from four previously conducted case-control studies within CCSS evaluating risk of subsequent neoplasms of the central nervous system (CNS),[7] breast,[8] and skin[9] as well as sarcoma.[10] The results of this analysis will provide a validation of appropriateness of the region-based radiation dose estimates for CCSS projects where detailed investigation of radiation dose-response relations is not the primary aim.

4. Specific Aims:

- Assess the agreement between the region-based radiation dose reconstruction and the detailed dosimetry to specific tumor locations conducted for patients from four previous case-control studies.
- Evaluate whether the agreement of the dose reconstruction methods varies by type of first primary cancer, age at first primary cancer diagnosis, year of first primary cancer diagnosis, or receipt of a specific radiotherapy treatment.

5. Analysis Framework:

Study Population:

Primary analyses will include patients from CCSS case-control studies evaluating risk of subsequent neoplasms of the CNS, [7] breast,[8] and skin[9] as well as sarcoma.[10] Eligibility criteria for each study have been described previously. Briefly, cases were diagnosed with incident, confirmed subsequent neoplasms of interest as of a specific date (CNS and breast: December 31, 2001, skin and sarcoma: February 1, 2007). Subsequent neoplasms were identified initially by self-report or reporting by next-of-kin on either the CCSS baseline questionnaire or one of the follow-up questionnaires administered every two-three years, or by periodic searches of the National Death Index. Subsequent neoplasm diagnoses were then confirmed through central review of pathology reports by CCSS investigators. If pathology reports could not be obtained, subsequent neoplasm diagnoses were determined by review of the initial questionnaire response, death certificate, and/or other institutional records. Four individually matched controls were selected randomly from the cohort for each case patient (except in the BCC study, which selected three controls per case), matching on age at first primary malignancy diagnosis, survival without subsequent neoplasm at least as long as the matched case's interval from first primary malignancy diagnosis to subsequent neoplasm diagnosis, and sex (except the BCC study). Within these study populations, we propose to exclude:

- patients with a known history of bone marrow transplantation who may have received total body irradiation,
- patients whose subsequent neoplasm occurred within five years of first primary malignancy diagnosis (because CCSS only systematically ascertained subsequent neoplasms occurring at least five years following first primary malignancy diagnosis),
- patients who were known to have received radiotherapy more than five years following first primary malignancy diagnosis (because detailed data on these radiotherapy treatments were not systematically collected), and
- patients who were diagnosed and perhaps treated for a subsequent neoplasm prior to the diagnosis of the subsequent neoplasm of interest (because treatment data for subsequent neoplasms were not systematically collected).

Secondary analyses that describe the distribution of radiation doses received to different regions of the body will include all CCSS participants (diagnosed 1970-1986) with information on radiotherapy treatments (see Example Table 1).

Exposure of Interest:

The exposures of interest are the radiation dose estimates to specific body regions or tumor locations from the two dose reconstruction methods. Both dose estimates are based on the same radiotherapy treatment data abstracted from medical records onto standardized forms, including information on dates of therapy; beam energy; field type, location, and size; use of radiation field blocks to protect normal tissue; and prescribed dose.

For the region-based dosimetry, radiation exposure was estimated as the maximum treatment dose to specific body regions, taking into account only direct in-beam contributions to that region. Dose estimates were based on field type and location (assuming standard blocking), beam energy, and prescribed dose, including treatments received within five years of first primary malignancy diagnosis because only treatments occurring during this time period were systematically collected for all CCSS participants. Regions not directly treated were classified as "scatter high" if the region of interest was adjacent to a treated region (with doses ranging from 0.5-5 Gy or 1-10% of the treatment dose) or "scatter low" if the region was interest was not adjacent to the treated region (with doses ranging from 0.001-1 Gy or <1% of the treatment dose).

For the case-control studies, radiation exposure was estimated as the mean dose to the specific location of the case's tumor (and corresponding location for matched controls). Dose estimates were based on individual-level data on field type, location, and size; blocking; beam energy; and prescribed dose, including all treatments for which data were available up to the time of subsequent neoplasm diagnosis. For the BCC study, a special program to estimate skin dose during radiotherapy was developed.[11]

Data on tumor location were comprehensively reviewed for the case-control studies as well as during the audit of all subsequent neoplasms that took place in 2012. The tumor location utilized for the case-control study will also be utilized for the purpose of this analysis.

Statistical Analysis:

The outcome of interest for this study is the agreement between the two radiation dose reconstruction methods. The following analyses will be conducted in the overall population, then repeated among patient subgroups defined by type of first primary malignancy, age or year of first primary malignancy diagnosis, tumor location (e.g., by brain segment, breast quadrant, etc.), receipt of a specific radiotherapy field (e.g., mantle field), and case/control status:

1. * Illustrate the relationship between the doses by plotting the region-based dose estimate versus the mean dose to the tumor location (see Example Figure 1).
2. * Compute the correlation between the region-based dose estimate and the mean dose to the tumor location (see Example Figure 1). The corresponding 95% confidence interval can be obtained using Fisher's r-to-z transformation.
3. * Compute the kappa statistic (percent agreement) between the region-based dose estimate and the mean dose to the tumor location, categorizing the doses into five groups as <1, 1-9.9, 10-19.9, 20-29.9, and 30+ Gy (see Example Tables 2-3).
4. Estimate the bias for our estimates of subsequent neoplasm risk when we use the region doses instead of the mean doses based on the results from #2 and 3 above. Furthermore, we will compare the effect size in the case control studies by estimating the odds ratio and 95% confidence interval according to radiation dose, categorized into five groups as <1, 1-9.9, 10-19.9, 20-29.9, and 30+ Gy (see Example Table 4), as well as the excess odds ratio per Gy, using the two different dose measures.

* Primary analyses for #1-3 will exclude patients who did not receive any radiotherapy and those with unknown radiation dose from either dose reconstruction method.

Specific tables/figures:

The following preliminary tables and figures present data from initial analyses of the agreement between the radiation dose reconstruction methods for CNS tumors, serving as examples of the types of tables and figures that may be generated from this analysis.

Example Table 1. Estimated maximum treatment doses to 4 segments of the brain for the entire cohort (N=14,370; the subset of patients included in case-control study has very similar proportions):

Dose category	Segment1	Segment2	Segment3	Segment4
0 Gy (no radiotherapy)	29.4%	29.4%	29.4%	29.4%
Scatter low (no direct treatment to the head)	24.9%	24.9%	24.9%	24.9%
Scatter high (direct treatment to the head but <50% of the segment was in the treatment field)	5.2%	3.2%	6.7%	6.9%
Known dose (0.1 to ~100 Gy; direct treatment to the head with ≥50% of the segment in the treatment field)	26.3%	28.3%	24.7%	24.6%
No info/unknown radiotherapy	14.2%	14.2%	14.2%	14.2%

Example Figure 1. Comparison of region dose (Gy, x-axis) to the mean dose to the specific location of the subsequent brain tumor (Gy, y-axis); r=0.95 (95% CI 0.94-0.96) for individuals in the previous case-control study[7] (applying the study population exclusions described above)
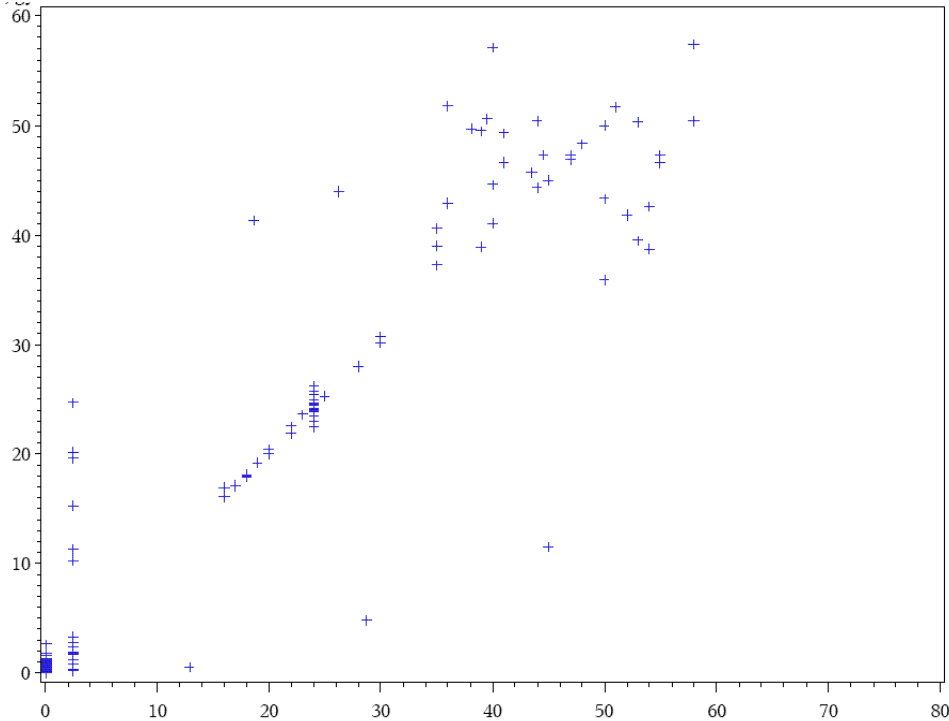
Example Table 2. Comparison of region dose to the mean dose to the specific location of the brain tumor for individuals in the previous case-control study[7] (applying the study population exclusions described above)

Mean dose to specific tumor location (Gy)	Region dose (Gy)					
	<1*	1-9.9**	10-19.9	20-29.9	30+	Total
<1	105	3	1	0	0	109
1-9.9	6	8	0	1	0	15
10-19.9	0	4	34	0	1	39
20-29.9	0	2	0	85	0	87
30+	0	0	1	1	37	39
Total	111	17	36	87	38	289

* Includes "scatter low"
** Includes "scatter high"

Example Table 3. Kappa (percent agreement) for two methods, using categories in Table 2

	Overall
Overall	0.90
Known tumor location, single brain segment	0.91
Known tumor location, multiple segments	0.81
Unknown tumor location	0.97

Example Table 4. Brain tumor risk according to radiation dose for individuals in the previous case-control study[7] (applying the study population exclusions described above)

Radiation dose (Gy)	Odds ratio (95% confidence interval)*	
	Mean dose to specific tumor location	Region dose
<1	1.0 Referent	1.0 Referent
1-9.9	4.1 (0.4-43.9)	13.2 (1.9-88.7)
10-19.9	12.9 (3.1-54.2)	12.0 (3.0-48.5)
20-29.9	22.7 (6.8-75.6)	21.1 (6.6-67.9)
30+	78.4 (20.6-297.5)	80.0 (21.2-302.0)
Unknown dose	6.3 (1.9-20.4)	31.6 (3.2-310.9)
Unknown RT	2.4 (0.2-25.2)	2.5 (0.2-26.9)

* Estimated using conditional logistic regression.

Study Limitations: Several sources of potential misclassification of the radiation dose estimates will be important to mention as limitations in any study that utilizes the region-based radiation dose estimates:
- Some patients received radiotherapy more than 5 years following first primary diagnosis (either for recurrence or treatment for subsequent neoplasm), because data on these treatments were not systematically collected.
- Tumor location may be poorly specified for some patients.
- Individual-level information on field configurations and blocking was not utilized because it is not feasible to take such detailed information into account in estimating radiation exposures across the entire body for a large cohort of patients.
- Only the maximum treatment dose to a region was considered. Mean dose across a region could not be estimated because dose estimates to all parts of the body were not specified due to lack of detailed information on field configurations and blocking.

6. Target Audience: The target audience for this work is a radiation journal such as *Radiation Research*.


7. References:

1.   Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/; 2011.
2.   Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2008;100(19):1368-1379.
3.   Reulen RC, Winter DL, Frobisher C, et al. Long-term cause-specific mortality among survivors of childhood cancer. *JAMA*. 2010;304(2):172-179.
4.   Armstrong GT, Liu W, Leisenring W, et al. Occurrence of multiple subsequent neoplasms in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2011;29(22):3056-3064.
5.   Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: The Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2010;102(14):1083-1095.
6.   Berrington de Gonzalez A, Gilbert E, Curtis R, et al. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. *Int J Radiat Oncol Biol Phys*. 2013;86(2):224-233.

7.   Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2006;98(21):1528-1537.

8.   Inskip PD, Robison LL, Stovall M, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. *J Clin Oncol*. 2009;27(24):3901-3907.

9.   Watt TC, Inskip PD, Stratton K, et al. Radiation-related risk of basal cell carcinoma: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2012;104(16):1240-1250.

10.   Henderson TO, Rajaraman P, Stovall M, et al. Risk factors associated with secondary sarcomas in childhood cancer survivors: a report from the childhood cancer survivor study. *Int J Radiat Oncol Biol Phys*. 2012;84(1):224-230.

11.   Kry SF, Smith SA, Weathers R, Stovall M. Skin dose during radiotherapy: a summary and general estimation technique. *J Appl Clin Med Phys*. 2012;13(3):3734.

Figure 1. Body region boundaries
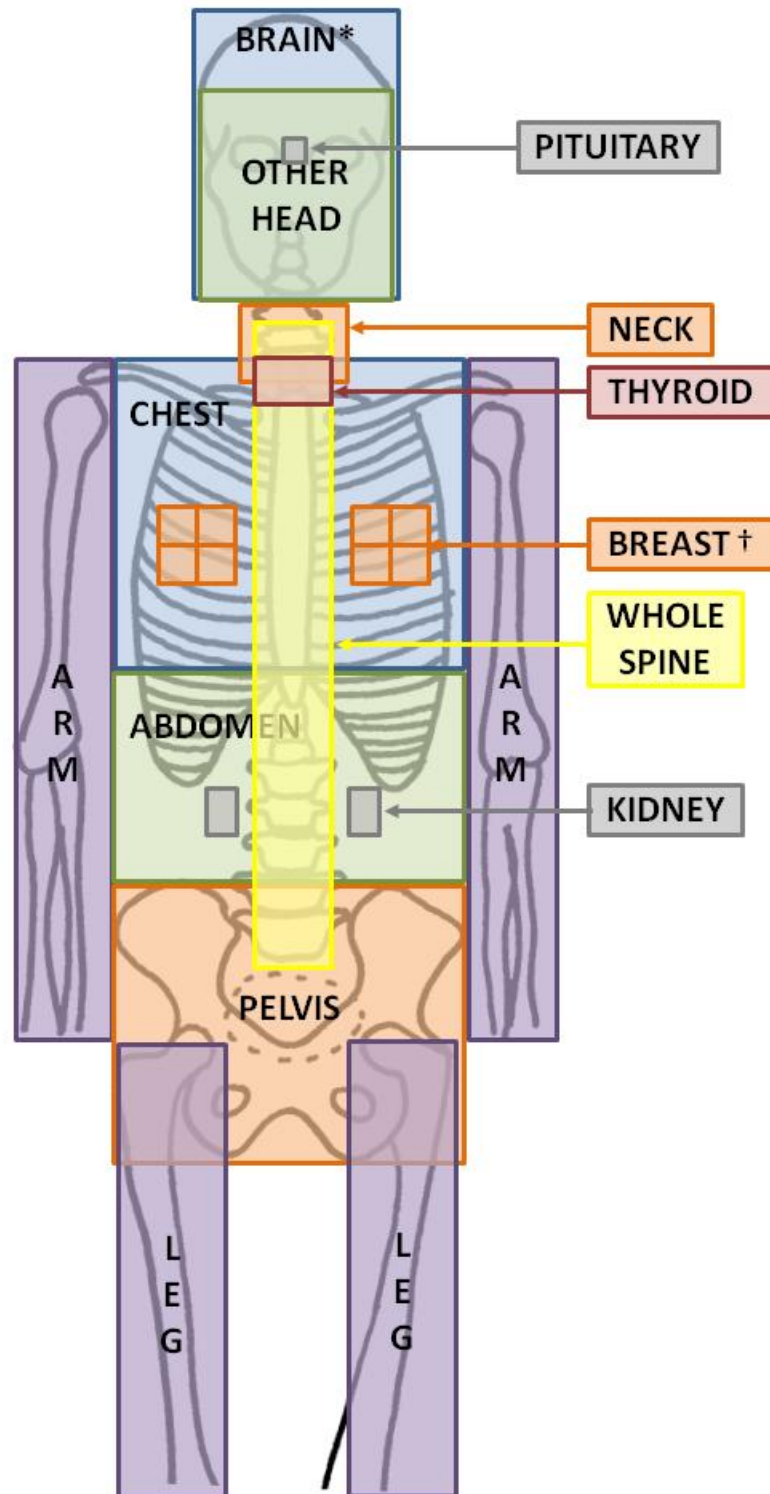
* See Figure 2 for brain region boundaries
† Doses were estimated to four quadrants of the breast only for patients who received a mantle field.

Figure 2. Brain region boundaries