CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

Study Title: Influence of Radiotherapy Dose to Cardiac Substructures on Cardiac Risk in Long-Term Survivors of Childhood Cancer

Working Group and Investigators: This proposed analysis will be within the Chronic Disease Working Group with secondary oversight by the Epidemiology/Biostatistics Working Group. Proposed investigators will include:

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Background and Rationale:
Over the past several decades, prognosis following a diagnosis of childhood cancer has drastically improved.[1] Simultaneously, awareness of the late toxicities of childhood cancer treatment has blossomed.[2-5] Cardiac disease is among the most common causes of severe or disabling chronic conditions and non-oncologic death in long-term survivors of childhood cancer.[3,5] Thoracic radiotherapy (RT) and anthracycline-based chemotherapy are known risk factors for late cardiac disease in these survivors; both show strong dose-response relationships (based simply on mean heart dose alone), with patients receiving the highest doses being at the greatest risk for cardiac disease.[6,7] While modern treatment protocols have resulted in decreased incidence of chronic health conditions overall, the incidence of severe or disabling cardiac disease has not changed in survivors diagnosed between the 1970s and 1990s.[8] Our primary hypothesis is that RT doses to various cardiac substructures will significantly better predict late cardiac toxicity in long-term survivors. Our findings may lead to clinically relevant prioritization of cardiac substructures during radiation planning for children newly diagnosed with a malignancy.

Current data establishing the dose-response relationship between RT and late cardiac disease are based on either the prescribed RT dose (assuming that it was delivered evenly to the entire heart) or the mean

heart RT dose.[6,7,9-12] These relationships have driven RT treatment design advances in order to reduce doses below levels associated with the greatest risk for late cardiac disease. However, the heart is not a homogenous organ; it is made of several distinct tissues that may have varying sensitivities to RT-induced late effects. These methods of quantifying the RT dose received by the entire heart do not adequately describe dose to the ventricles, atria, coronary arteries, or valves.

Different exposures to various cardiac substructures likely confer different risk profiles. The foundational Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) analysis, which established standard cardiac dose constraints, identified the correlation between substructure doses and clinical outcomes as a vital area of future research.[13] Data evaluating these relationships are nonexistent in a purely pediatric population and are sparse in older populations. An analysis of adult survivors of Hodgkin lymphoma (median age at diagnosis 31 years (range: 18-75 years) treated with RT found that doses to the coronary arteries better predicted ischemic heart disease than whole-heart RT doses.[14] A review of Dutch Hodgkin lymphoma survivors across the age spectrum found a nonlinear dose-response relationship between mean heart dose and risk for heart failure with minimal risk below a mean dose of 25 Gy. However, the dose-response relationship was linear when evaluating mean left ventricular dose with no threshold and a 9.0% increase in heart failure risk per 1 Gy increase in mean left ventricular dose.[15] A separate, small analysis of adolescent and young adult survivors of Hodgkin lymphoma showed that only patients who received doses beyond 30 Gy to the cardiac valves experienced a substantially increased risk of valvular disease.[16] This contrasts with an analysis of the Childhood Cancer Survivor Study (CCSS), which showed a tripling in risk of valvular disease at mean heart RT doses of 15 – 35 Gy.[6] While these represent different populations, the difference in risk thresholds is striking and strongly suggests that mean heart doses do not provide a complete picture of RT-related cardiac risk. There is clearly a need to better describe these relationships across the various cardiac substructures to elucidate the cardiac risks caused by RT.

Modern RT dose constraints and treatment protocol designs aimed at reducing late cardiac morbidity have been driven by whole-heart dose metrics; hence, this may help explain our lack of progress in reducing the burden of chronic cardiac conditions in childhood cancer survivors.[8] We believe that elucidating the dose-response relationship between cardiac substructures and the risk for specific late cardiac diseases will revolutionize the constraints used to develop RT delivery plans and treatment protocols for children with cancer. Furthermore, improved knowledge of individual risks for specific cardiac diseases will improve potential screening strategies for current and future survivors of childhood cancer.

Specific Aims/Objectives/Research Hypotheses:
Specific Aim #1: Refine the heart model of current CCSS age-specific computational phantoms by defining cardiac substructures (i.e., left ventricle, right ventricle, left atrium, right atrium, cardiac valves, and coronary arteries) such that mean and maximum doses can be determined for each structure.

Specific Aim #2: Compute the mean and maximum dose to each of the cardiac substructures defined in aim 1.

Multiple epidemiological studies have been published using RT dose reconstructions performed on the CCSS cohort, including our own analysis of cardiac late effects using whole-heart dose metrics.[6, 19-21] The MD Anderson Late Effects Group pioneered the general methodology for dose reconstructions used by the CCSS.[17,18] This methodology has become widely accepted and was used for RT dose reconstruction in Dutch and Scandinavian cohorts of childhood cancer survivors.[24,25]

While previous CCSS studies have subdivided specific organs in to three (pancreas, esophagus) or four (brain) regions, no prior analysis has subdivided an organ to the degree that we propose.[18,26,27] We will modify the phantom by significantly increasing the number of calculation points within the region of the heart to dramatically enhance the resolution of dose calculations. We will then use anatomic atlases to group specific points into a variety of cardiac substructures, including the bilateral ventricles, bilateral atria, coronary arteries (left anterior descending, left circumflex, left main, and right coronary arteries), all fourcardiac valves, and the pericardium. This evolution is shown in **Figure 1**. Thereafter, doses will be computed to each point within the phantom for each patient within the CCSS cohort receiving RT. We will take the average dose to each point within each substructure to determine the average dose to that substructure. Likewise, we will estimate the maximum dose to each substructure based on the highest dose received by a point within a given substructure. For larger substructures (the atria and ventricles), we will also determine the percentage of the volume of said substructure receiving specific doses of RT (5 Gy and 20 Gy) based on the number of points receiving greater than or equal to that dose.

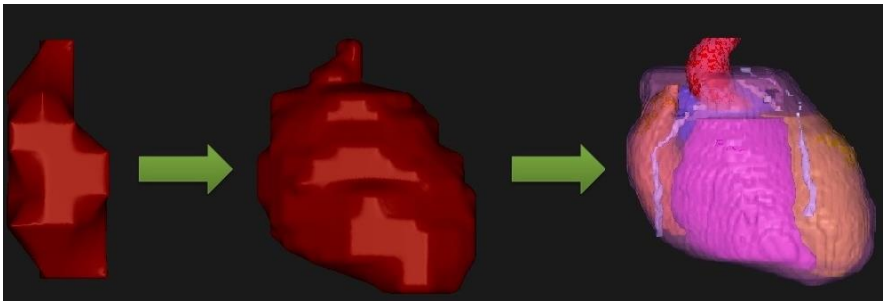

Figure 1. Evolution of CCSS heart phantom from old heart (55 points, left), to new heart (1230 points, middle), to new heart with substructures delineated (right).

<u>Specific Aim #3</u>: Evaluate the relationships between radiation dose to specific substructures and the risk of specific Common Terminology Criteria for Adverse Events (CTCAE) grade 3 – 5 cardiac toxicities (i.e., coronary artery disease, heart failure, valvular disease, arrhythmias, and pericardial disease) in long-term survivors of childhood cancer.

We will use multivariable Cox regression models to determine adjusted hazard ratios of developing CTCAE grade 3 – 5 (corresponding to severe, life-threatening, or fatal) cardiac diseases in five-year survivors of childhood cancer by specific cardiac substructure dose-volume metrics. Other variables in these models will correspond to other known risk factors for cardiac disease, including, but not limited to, age, sex, race/ethnicity, anthracycline dose, and cisplatin dose. We identified these variables as risk factors for cardiac disease in our previous analysis of whole-heart dose metrics.[21] We may also analyze the impact of other known risk factors for cardiac disease including smoking status, high blood pressure,

and obesity. The specific outcomes analyzed will include coronary artery disease, heart failure, valvular disease, arrhythmia, and pericardial disease.

We will generate models for (1) a combined endpoint of developing any cardiac disease and (2) each specific cardiac disease. For example, we will generate a model investigating the dose-response relationship between mean and/or maximum RT dose to the cardiac valves and risk of valvular disease. Likewise, we will generate a model investigating the relationship between left ventricular dose metrics (including mean dose and percentage volumes of the left ventricle receiving 5 Gy and 20 Gy) and heart failure. The volume of whole heart receiving 5 Gy and 20 Gy was found to be associated with risk for late cardiac disease in a previous analysis. Another potential relationship we will investigate is relationship between the individual coronary arteries and risk of coronary artery disease and/orheart failure. Additionally, for relevant endpoints where our modeling reveals clinically meaningful relationships between RT dose metrics to cardiac substructures and risk of late cardiac disease, we will compare the cumulative incidences of cardiac disease in the relevant cohort populations to the sibling population to carry out absolute excess risk calculations. This will enable a better epidemiological understanding of the true risks of specific RT doses in this high-risk population and will help drive evidence-based cardiac disease-screening strategies.

Specific Aim #4: Generate multivariable models to identify the most predictive radiation dose metrics of overall and specific CTCAE grade 3 – 5 cardiac toxicities in long-term survivors of childhood cancer.

Following the evaluation of numerous dose-response relationships between cardiac RT doses to specific substructures and risk for late cardiac diseases in long-term survivors of childhood cancer, we will determine which dose metrics (single or in combination) are most predictive of late cardiac disease to help guide RT treatment planning for future children with cancer. Multivariable Cox regression models, using all available potential predictors, including RT doses to specific substructures, other treatment variables (e.g., anthracycline dose), clinical characteristics (e.g., cancer subtype, age at diagnosis), and demographic characteristics (age, sex, race/ethnicity), will be constructed for the purpose of predicting incidence of any and specific CTCAE grade 3-5 cardiac events.[28] The discriminatory and predictive performance of each model will be measured by the area under the curve (AUC) at age 40 or 50 years and the concordance (C) statistic (weighted average of AUC from the follow-up start of CCSS at 5 years since cancer diagnosis through age 40 or 50 years) designed for time-to-event outcomes.[29] The values of these metrics around 0.5 suggest that a model predicts no better than chance, and values approaching 1 indicate perfect discrimination and prediction. To minimize overfitting, we will consider Lasso and other modern model-selection methods, and the AUC and C will be cross-validated (10-fold) by randomly partitioning the CCSS cohort into ten subsets.[30] Candidate models for overall and specific cardiac disease risks will be generated using the methodology described above. This will generate six “best fit” models for RT dose parameters: one for the composite cardiac disease endpoint and one each for the five specific cardiac diseases that we will evaluate. If robust, these models will immediately impact clinical practice for pediatric radiation oncologists. They will guide definition of dose constraints to the cardiac substructures, which are critical for the design of modern RT treatment plans, and will help inform which patients will benefit most from advances in radiation technology. Furthermore, these models will

improve our ability to identify survivors who would benefit most from enhanced screening regimens to potentially improve the likelihood of early detection of any late cardiac disease.

Analysis Framework:
Population: All survivors in the CCSS baseline and expanded cohort who completed at least the baseline evaluation. The sibling population may also be used to determine absolute excess risks.

Exposures of Interest: Radiation doses to various cardiac substructures (ventricles, atria, cardiac valves, coronary arteries), mean cardiac radiation dose, the percentage volume of the heart receiving 5 Gy (cardiac V5), the percentage volume of the heart receiving 20 Gy (cardiac V20), cumulative anthracycline dose, cumulative cisplatin dose, and alkylating agent exposure.

Outcome(s) of Interest: The primary outcome of interest will be grade 3-5 heart failure, coronary artery disease, arrhythmias, pericardial disease, and valvular disease (as graded per the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0). These will be based on patient self-report on the baseline, 2000 follow-up, 2007 follow-up, or other subsequent follow-up surveys.

Adjustment Variables:

- Gender
- Race
- Ethnicity
- Age at Diagnosis
- Attained Age
- Year of Initial Diagnosis
- Primary Cancer Diagnosis
- Alkylating Agent Use (yes/no)

Tables:
Table 1. Patient Characteristics (n = ***)

	All Patients (n = ***)	**Patients Receiving >0.1 Gy Mean Cardiac RT Dose** (n = ***)
Variable	**Number (%)**	**Number (%)**
Age at Diagnosis		
Age at Last Follow-up		
Gender		
Male		
Female		
Race		
White		
Black		
Other		

Ethnicity		
Hispanic		
Non-Hispanic		
Primary Cancer Diagnosis		
Leukemia		
HL		
NHL		
CNS		
Wilms Tumor		
Neuroblastoma		
Rhabdomyosarcoma		
NRSTS Bone sarcomas		
Other		
Smoking Status		
Smoker		
Never Smoker		
Cumulative Anthracycline Dose		
None		
1 – 249 mg/m^2		
≥250 mg/m^2		
Cumulative Cisplatin Dose		
None		
1 – 299 mg/m^2		
≥300 mg/m^2		
Alkylating Agent Exposure		
Yes		
No		
Volume of Heart Receiving 5 Gy when V20 = 0% ($V5_{V20=0\%}$)		
No RT		
0%		
0.1 – 49.9%		
$\geq$50%		
Volume of Heart Receiving 20 Gy		
No RT		
0%		
0.1 – 29.9%		
30 – 79.9%		
$\geq$80%		

Table 2. Incidence rates/hazard ratios of various cardiac disease by various cardiac substructure dose metrics

	Any Cardiac Disease				Coronary Artery Disease				Heart Failure			
Mean LV Dose	30yr Cumulative Incidence	Adjusted RR	95% CI	P value	30yr Cumulative Incidence	Adjusted RR	95% CI	P value	30yr Cumulative Incidence	Adjusted RR	95% CI	P value
0 Gy												
0.1 – 5 Gy												
5.1 – 15 Gy												
15.1 – 25 Gy												
>25 Gy												
	Valvular Disease				Pericardial Disease				Arrhythmia			
Mean LV Dose	30yr Cumulative Incidence	Adjusted RR	95% CI	P value	30yr Cumulative Incidence	Adjusted RR	95% CI	P value	30yr Cumulative Incidence	Adjusted RR	95% CI	P value
0 Gy												
0.1 – 5 Gy												
5.1 – 15 Gy												
15.1 – 25 Gy												
>25 Gy												

LV = left ventricle

RR = rate ratio

CI = confidence interval

- A table similar to this will be made for mean heart dose and each individual cardiac substructure
- Doses cutoffs will be determined for each individual substructure once the dose distributions to those substructures are known
- The final selection of tables will be dependent on which substructures have meaningful relationships with late cardiac disease

Table 3. AUC Results – will display the “best-fit” models for predicting cardiac disease

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