CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

Study Title: The Impact of Developmental Status on Radiation-associated Late Cardiac Toxicities in Long-Term Survivors of Childhood Cancer

Working Group and Investigators: This proposed publication 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:

Due to the many advances in pediatric oncologic therapy, the vast majority of children newly diagnosed with cancer will become long-term survivors; however, most will also develop at least one chronic health condition by the age of 40 [1]. Cardiac disease is among the most common severe, disabling, life-threatening, or fatal chronic health condition found among long-term survivors of childhood cancer who have a 6.9-fold increase in the risk developing these conditions relative to their siblings [2]. Cardiovascular disease is the most common treatment-related non-cancer cause of death among long-term survivors of pediatric cancer [3]. Additionally, recent research suggests nearly one in three long-term survivors of childhood cancer exposed to either anthracycline-based chemotherapy or chest radiotherapy had

echocardiographic evidence of heart dysfunction despite a normal left ventricular ejection fraction [4].

Previous analysis of the Childhood Cancer Survivor Study (CCSS) cohort has shown that among long-term survivors, those initially diagnosed at ages 0-4 years and 5-9 years were significantly more likely to develop congestive heart failure (HR = 3.9, $p < 0.001$; HR = 2.3, $p = 0.004$) and valvular abnormalities (HR = 2.7, $p = 0.004$; HR = 2.5, $p = 0.001$) when compared to those aged 15-20 years at time of initial diagnosis. Increasing average cardiac radiation doses were also associated with increased risk for the long-term development of congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities [5].

Based on the development of the human heart, there is some evidence that there may be a difference in radiation dose sensitivity among various aged children. While the number of cardiomyocytes is essentially stable from birth to death, the majority of cardiomyocyte turnover occurs in the first decade of life. By age 10, 80% of the cardiomyocytes will never be exchanged. The second decade of life is dominated by ploidization in the cardiomyocytes. The DNA content of cardiomyocytes increases 1.7-fold in the left ventricle and 1.6-fold in the right ventricle during the second decade of life and remains constant thereafter [6]. Damage to cardiomyocytes has been traditionally seen as an indirect effect of cardiac radiation driven primarily by damage to the microvasculature as cardiomyocytes are terminally differentiated [7]. This evidence of cellular turnover early in the lifespan may suggest that direct cardiomyocyte toxicity may play a role in the development of late cardiac effects in children treated with radiotherapy.

Beyond cardiomyocytes, damage to cardiac mesenchymal and endothelial cells play a major role in the development of late effects of radiation. Both of these cell types undergo a rapid period of growth during the first 20-30 years of life and slowly decline in number thereafter [6]. Endothelial damage is thought to be the primary driver of late, radiation-related cardiovascular disease. Proteomic analysis of mice exposed to cardiac radiation showed upregulation of proteins involved in endothelial senescence and alterations in both cytoskeletal proteins and extracellular adhesion molecules [8]. Early disruption of the cardiac microvasculature through radiation-induced endothelial dysfunction could place young children particularly at risk for late cardiac effects.

The increased risk of late cardiac dysfunction in children under the age of 4 years receiving anthracycline-based chemotherapy relative to older children has been reasonably well established [9]. However, no data exists to define the role age of treatment plays in the development of late cardiac toxicities among children receiving any radiation to their heart. This analysis proposes to define dose-response curves for cardiac radiation and cumulative late cardiac toxicities as scored by the Common Terminology Criteria for Adverse Events (CTCAE)

version 4 criteria among various age groups according to age at initial diagnosis in order to determine developmental periods of increased risk for radiation-related cardiac late toxicities.

Specific Aims/Objectives/Research Hypotheses:

Aim 1: Compare the dose-response relationship between cardiac radiation and the development of specific grade 3-5 late cardiac toxicities (congestive heart failure (CHF), coronary artery disease/myocardial infarction (CAD/MI), arrhythmias, pericardial disease, and valvular disease) overall and among groups of children at varying ages at initial diagnosis to identify ages of highest risk for late cardiac toxicity development.

Hypothesis: The dose-response relationship will identify increased risk of late cardiovascular effects, as measured by CTCAEv4 criteria, for survivors at younger ages receiving the same cardiac radiation dose as older individuals. This effect will be most pronounced for CHF and valvular disease.

Aim 2: Compare the dose-response relationship between anthracycline dose and the development of specific grade 3-5 late cardiac toxicities (CHF, CAD/MI, pericardial disease, and valvular disease) overall and among groups of children at varying ages of initial diagnosis.

Hypothesis: The dose-response relationship will identify increased risk of late cardiac effects (specifically, CHF) for survivors at younger ages receiving the same anthracycline dose as measured by the CTCAE v4 criteria.

Aim 3: To determine whether there is an interaction between cardiac radiation, anthracycline dose and age, such as would increase risk for late cardiac toxicities beyond what would be expected under an additive hypothesis.

Hypothesis: There will be a synergistic effect between age at diagnosis, cardiac radiation, and anthracycline dose on cardiac late effects. This will be most pronounced for the development of CHF.

Analysis Framework:

Population: All survivors in the CCSS who completed at least the baseline evaluation.

Exposures of Interest: Age at diagnosis, mean cardiac radiation dose, and cumulative anthracycline dose

Outcome(s) of Interest: The primary outcome of interest will be specific late cardiac toxicities reported on the baseline, 2000 follow-up, or 2007 follow-up survey. Those toxicities will include CHF, CAD/MI, arrhythmias, pericardial disease, and valvular disease. Severity will be defined per the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 as previously

performed and reported by Oeffinger, et al and Armstrong, et al [2, 10]. Additionally, specific late cardiac effects will be analyzed separately including the development of congestive heart failure, myocardial infarction, pericardial disease, and valvular disease

Adjustment Variables:

Gender
Ethnicity
Age at Interview
Years since diagnosis
Year of Initial Malignancy
Primary Cancer Diagnosis
Alkylating Agent Use (yes/no)
Platinum Agent Use (yes/no)

The treatment-related variables above will include treatments received within 5 years from the diagnosis, prior to the CCSS cohort entry.

Statistical Analysis:

Aim 1: Patients will be split into four (or two if the outcome count does not permit four) groupings based on age at initial diagnosis for analysis (0-4 years, 5-9 years, 10-14 years, 15-20 years). Within each age group of patients, for each type of cardiovascular late effect (CHF, CAD/MI, arrhythmias, valvular disease, pericardial disease), we will calculate/estimate the cumulative incidence curve overall and stratify by cardiac radiation dose, calculated as previously described [11]. This serves as the descriptive analysis of each outcome with respect to two of the three exposure variables of interest (age at diagnosis and mean cardiac radiation dose).

Incidence rate analysis will be performed using piecewise exponential regression for each grouping of grade 3 – 5 CTCAE cardiovascular events. Person years at risk will start at the CCSS cohort entry (if the event of interest developed before the cohort entry, the subject will be removed from the analysis) and end at the earliest of the development of the event of interest, death, or the last questionnaire completion. The model will include age at diagnosis, mean cardiac radiation dose, and the adjustment variables listed above: this model will be adjusted for anthracycline dose. The parameters of interest would be those that characterize the dose-response relationship of mean cardiac radiation dose and the incidence rate of the event of interest in each age-at-diagnosis group: this will be represented as an effect modification of mean cardiac radiation dose by age at diagnosis.

Graphical as well as tabular representations of the model fits will be used to clearly communicate the complex nature of the effect modifications.

Aim 2: This will use exactly the same approach as Aim 1, replacing mean cardiac radiation dose with anthracycline dose.

Aim 3: The goal of Aims 1 and 2 are to understand the effect modifications of mean cardiac radiation dose and anthracycline exposures, respectively, by age at diagnosis. Aim 3 will synthesize them and explore the potential that mean cardiac radiation dose and anthracycline dose interact, either similarly or differently across the different age-at-diagnosis groups. Methodologically, this will be assessed using the relevant 2-way and 3-way interaction terms of the three exposure variables of interest in the same piecewise exponential regression, adjusting for the adjustment variables above.

Tables:

Table 1. Patient Characteristics (n = *)

	All Patients (n = *)	**Patients with >0.1Gy mean cardiac RT (n = *)**	**Patients with ≥1 mg/m² cumulative anthracycline dose (n = *)**
Variable	**Number (Percentage) or Median (Range)**	**Number (Percentage) or Median (Range)**	**Number (Percentage) or Median (Range)**
Age at Initial Diagnosis			
Age at Last Follow-up			
Duration of Follow-up			
Calendar Year of Initial Diagnosis			
Gender			
Male			
Female			
Ethnicity			
Caucasian			
African-American			
Other			
Primary Cancer Diagnosis			
Leukemia			
HL			
NHL			
Neuroblastoma			

Other			
Mean Cardiac Radiation Dose			
None			
<5 Gy			
5 Gy - <15 Gy			
15 Gy - <25 Gy			
25 Gy - <35 Gy			
35 Gy - <45 Gy			
≥45 Gy			
Cumulative Anthracycline Dose			
None			
1 – 100 mg/m^2			
101 – 200 mg/m^2			
201 – 300 mg/m^2			
301 – 400 mg/m^2			
401 – 500 mg/m^2			
>500 mg/m^2			

Table 2: Incidence rates of various cardiovascular chronic health conditions by age at diagnosis

(a) Stratified by mean cardiac radiation dose dose

(b) Stratified by anthracycline dose

Table 3. Piecewise exponential regression results

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