Cardiac Substructure Dose and Late Cardiac Disease: Report from the Childhood Cancer Survivor Study

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Purpose/Objective:

Most children diagnosed with cancer become long-term survivors; however, many develop at least one severe, life-threatening, or fatal complication related to their prior therapy. Cardiac disease is among the most common of these late complications. We previously identified dose-response relationships between radiation dose to cardiac substructures (chambers, vessels, valves) that were more sensitive at predicting specific cardiac disease outcomes (e.g., heart failure [HF], coronary artery disease [CAD], arrhythmia, and valvular disease [VD]) than mean whole heart dose. We aimed to enrich the currently limited data regarding these relationships considering any late-onset (>5 years from diagnosis) cardiac disease as a composite outcome. This may help the contemporary radiation oncologist minimize the total burden of cardiac disease in survivors of childhood cancer. We evaluated this relationship among long-term survivors participating in the Childhood Cancer Survivor Study (CCSS).

Material/Methods:

We determined the cumulative incidence of Common Terminology Criteria for Adverse Events (CTCAE) for any grade 3 – 5 (severe, life-threatening, or fatal) cardiac disease among 25,481 five-year survivors of childhood cancer diagnosed before the age of 21 between 1970 and 1999 diagnosed at 31 institutions across the United States and Canada. Cardiac disease included HF, CAD, arrhythmia, and VD. Median age at cancer diagnosis was 6.1 years (range 0 – 20 years) and median age at last follow-up was 29.8 years (range 5.6 – 65.9 years). Treatment fields were reconstructed on age-scaled phantoms for all survivors exposed to radiation (n = 12,228). We calculated mean radiation doses to the whole heart, four chambers, four valves, and major coronary arteries (left anterior descending (LAD), circumflex, left main, and right coronary (RCA)). Excess relative rate (ERR) and piecewise exponential models, adjusted for demographic and treatment-related characteristics including the total anthracycline dose, were used to assess the dose-response relationships between radiation dose to various cardiac substructures and risk of any cardiac disease. Additionally, each substructure was individually added to a model with mean whole heart radiation dose and its statistical significance was assessed via the likelihood-ratio test to ascertain which substructures improved prediction of cardiac risk beyond whole heart dose.

Results:
The 35-year cumulative incidence of any cardiac disease was 7.0% (95% CI 6.5% – 7.6%). Using linear ERR modeling, for each 1 Gy increase in mean whole heart radiation dose, there was a 14.9% increase in risk of any cardiac disease. A quadratic model improved the fit relative to a linear model ($p < 0.001$, **Figure 1A**), suggesting a potential threshold dose below which there is no increased risk. However, for most substructure doses (LAD – **Figure 1B**, circumflex, RCA, left atrium, all valves, and right ventricle), a quadratic model did not improve its fit, suggesting no threshold dose below which there is no increased risk.

We added each mean substructure RT dose individually to a model including mean whole heart RT dose to identify which substructure dose may be most useful in combination with mean whole heart RT dose at improving prediction of late cardiac disease. Adding mean LAD dose to a model including mean whole heart dose improved model fit to the greatest degree ($\chi^2 = 29.1$, $p < 0.001$). Even among patients with a mean heart dose <5 Gy, a mean LAD dose of 10 – 19 Gy increased the risk of any cardiac disease (RR 3.3 95% CI 1.8 – 6.2, $p < 0.001$, **Table 1**).

Conclusion:
Considering cardiac substructure doses (especially the LAD) in addition to mean whole heart doses may enhance prediction of late cardiac morbidity in survivors of childhood cancer. When

developing pediatric treatment plans, radiation oncologists should consider doses to the cardiac substructures to minimize late cardiac risk.

Table 1. Risk of Any Cardiac Disease by Mean Radiation Dose to the Whole Heart and Left Anterior Descending Coronary Artery

		Mean Left Anterior Descending Coronary Artery Dose (Gy)					
		No RT	**<5**	**5 – 9.9**	**10 – 19.9**	**20 – 29.9**	**≥30**
Mean whole heart radiation dose (Gy)	**No RT**	Ref					
	<5		0.9 (0.7 - 1.2)	1.6 (0.9 - 3.1)	3.3 (1.8 - 6.2)*		
	5 – 9.9		0.6 (0.3 - 1.2)	1.1 (0.6 - 2.0)	2.3 (1.3 - 4.1)*		
	10 – 19.9		0.8 (0.4 - 1.5)	1.4 (1.0 - 2.2)	3.0 (2.3 - 3.8)*	3.2 (2.2 - 4.8)*	4.7 (2.8 - 7.8)*
	20 – 29.9				4.2 (2.8 - 6.3)*	4.6 (3.5 - 6.0)*	6.6 (4.5 - 9.9)*
	≥30					4.3 (2.7 - 6.9)*	6.2 (4.7 - 8.1)*

* represents statistically significant at the $p < 0.05$ level