Volumetric Dose-Effect Analysis of Late Cardiotoxicity: A Report from the Childhood Cancer Survivor Study (CCSS)

Purpose/Objectives: Cardiovascular disease (CVD) is the most common non-cancer cause of death among long-term survivors of pediatric cancer. We examined radiotherapy (RT) volumetric dose data to improve our understanding of RT-associated CVD risk in long-term survivors of childhood cancer.

Materials/Methods: We evaluated grade 3 – 5 cardiovascular events as defined by the Common Terminology Criteria for Adverse Events among 23,465 five-year survivors of childhood cancer diagnosed from 1970 to 1999. For survivors who received cardiac RT, we estimated heart doses for each individual in age-specific computational phantoms based on detailed abstraction of each patient's RT records. We estimated the percent volume receiving ≥5 Gy (V5) and ≥20 Gy (V20). The overall rates of developing any CVD, including heart failure (HF) or coronary artery disease (CAD), were estimated. Modifications of treatment effects by age at diagnosis were evaluated using piecewise exponential models adjusting for current age, race, and anthracycline use.

Results: At a median age of 28.4 years (range, 5.6 – 58.3) and time from diagnosis of 20.2 years (range, 5.0 – 39.3), 239 CAD and 359 HF events occurred. The cumulative incidence estimates of CVD, CAD, and HF were 4.8% (95% CI 4.3-5.3), 2.4% (95% CI 2.2-2.9), and 2.5% (95% CI 2.2-2.9), respectively, at 30 years from diagnosis. As shown in the table below, at a V20 of 0.1 – <25%, the risk for CVD was increased, primarily due to HF. The risk of CVD was greatest in those with a V20 of ≥50%, and not associated with age at diagnosis. To separately consider patients who received low-dose cardiac RT, we examined V5 in patients with a V20 of 0%. Those with a V5 of ≥50% and a V20 of 0% had an increased risk of CVD (RR, 1.7; 95% CI, 1.2 – 2.4; p = 0.004) compared to those with a V5 of 0%. The risk in this subset of patients was also not associated with age at diagnosis. Increased risk was not seen with lower V5 percentages.

Conclusions: Cardiac RT dose of 20 Gy or more, even to a low volume, substantially increased the risk for CVD, with further increased risk at V20 ≥50%. Additionally, survivors who received large-volume, low-dose cardiac RT (V5 ≥ 50% and V20 = 0%) had an increased risk for CVD. Age at diagnosis did not significantly impact the risk for CVD in this volumetric analysis. These results should guide future surveillance and treatment protocols.

	CAD		**HF**		**Any CVD**	
V20 of Heart	*RR (95% CI)*	*P value*	*RR (95% CI)*	*P value*	*RR (95% CI)*	*P value*
0%	Ref		Ref		Ref	
0.1 - <25%	1.8 (0.6 - 5.6)	0.34	3.0 (1.4 - 6.5)	0.004	2.5 (1.3 - 4.6)	0.005
25% - <50%	1.9 (0.8 - 4.8)	0.15	2.1 (0.9 - 4.8)	0.08	2.4 (1.4 - 4.2)	0.002
≥50%	5.4 (3.9 - 7.3)	<.001	5.7 (4.3 - 7.6)	<.001	5.2 (4.2 - 6.4)	<.001