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James E Bates, Suman Shrestha, Qi Liu, Daniel A. Mulrooney, Susan A Smith, Wendy M Leisenring, Todd Gibson, Eric J Chow, Kevin C Oeffinger, Leslie L Robison, Gregory T Armstrong, Louis S Constine, Bradford S Hoppe, Choonsik Lee, Yutaka Yasui, Rebecca Howell

Low Dose Radiation to Cardiac Substructures and Late Onset Cardiac Disease: A Report from the Childhood Cancer Survivor Study (CCSS)

Background:

Thoracic radiotherapy (RT) is a risk factor for cardiac disease among survivors of childhood cancer based on studies considering RT doses to the entire heart. Dose to specific cardiac substructures may provide more precise dose-response associations to guide RT planning. We report associations between RT dose to cardiac substructures and risk of specific cardiac outcomes.

Methods:

We determined the cumulative incidences of CTCAE grade 3 – 5 coronary artery disease (CAD), heart failure (HF), and valvular disease (VD) among 25,481 5-year childhood cancer survivors diagnosed 1970 – 1999 in the CCSS. Median age at diagnosis was 6.1 years (0 – 20 years) and at last follow-up 29.8 years (5.6 – 65.9 years). For the 12,228 individuals receiving RT, fields were reconstructed on an age scaled computational phantom. Mean doses to the entire heart, cardiac chambers, valves, and left main, anterior descending (LAD), circumflex, and right coronary (RCA) arteries were estimated. Adjusted piecewise exponential models (including cumulative anthracycline dose) evaluated associations between mean RT dose to each structure and outcomes.

Results:

At 30 years from diagnosis, the cumulative incidences of grades 3 – 5 CAD, HF, and VD were 2.3% (95% CI 2.0 – 2.5), 2.6% (95% CI 2.4 – 2.9), and 0.6% (95% CI 0.5 – 0.8) respectively. Low dose RT (mean 5 – 9.9 Gy) to the RCA (relative rate [RR] = 2.6, 95% CI 1.6 – 4.1, $p < 0.001$), LAD

(RR = 1.9, 95% CI 1.1 – 3.3, p = 0.019), and left ventricle (RR = 2.2, 95% CI 1.3 – 3.7, p = 0.002) was associated with increased risk of CAD relative to those not exposed; mean dose of 5 – 9.9 Gy to the entire heart was not (RR = 1.1, 95% CI = 0.8 – 1.6, p = 0.59). **Table 1** shows the associated cumulative incidences of CAD for these structures. Mean RT doses of 5 – 9.9 Gy to the aortic valve (RR = 4.6, 95% CI 1.5 – 14.0, p = 0.008) and tricuspid valve (RR = 5.5, 95% CI 2.0 – 15.1, p = 0.001) were associated with risk of VD compared to those with no RT; mean heart dose 5 – 9.9 Gy was not (RR = 0.6, 95% CI = 0.2 – 1.3, p = 0.16). No cardiac structure was significantly associated with an increased risk of HF at a mean dose of 5 – 9.9 Gy. Mean RT doses below 5 Gy were not associated with increased risks of CAD, HF, or VD; doses ≥10 Gy to nearly all substructures and the entire heart were.

Conclusions:

Low dose RT to the coronary arteries and cardiac valves (5 – 9.9 Gy) from RT is associated with increased risk of CAD and VD, respectively. Sensitivity to low dose RT may vary across the heart and doses to specific structures may be more predictive of late cardiac disease than whole heart dose. These data can guide RT planning to prioritize substructures for avoidance.

Table 1. 30-year cumulative incidence for CAD with low dose RT to selected cardiac substructures

Structure	**Mean RT Dose**	**CI (95% CI)**
Entire Heart	None	0.9% (0.6 – 1.2%)
Entire Heart	5 – 9.9 Gy	1.0% (0.2 – 1.8%)
RCA	5 – 9.9 Gy	2.6% (1.4 – 3.7%)
LAD	5 – 9.9 Gy	1.7% (0.8 – 2.7%)
Left ventricle	5 – 9.9 Gy	2.3% (1.1 – 3.5%)