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**Impact of Cardiac Substructure Dosimetry on Late Cardiac Risk: A Report from the Childhood Cancer Survivor Study (CCSS)**

*Purpose/Objectives*:

Prior estimates of radiation (RT)-associated cardiac disease risk in childhood cancer survivors are based on estimates of RT dose to the entire heart. We aimed to evaluate whether cardiac substructure RT dosimetry improves estimation of late cardiac disease risk.

*Materials/Methods*:

We determined the cumulative incidence of CTCAE grade 3 – 5 cardiac disease (heart failure, coronary artery disease, valvular disease, arrhythmia, or pericardial disease) among 25,481 5-year survivors from CCSS diagnosed 1970 – 1999. Median age at diagnosis was 6.1 years (range 0 – 20) and at last follow-up was 29.8 years (5.6 – 65.9). We considered a single composite endpoint of any cardiac disease to best identify which substructures to prioritize for avoidance in RT planning to minimize the absolute risk of cardiac disease. We reconstructed RT fields for irradiated survivors (n = 12,228) on an age-scaled phantom and estimated mean RT dose to the heart, four chambers, four valves, and the left anterior descending (LAD), circumflex, main (LM), and right coronary arteries. Adjusted piecewise exponential models (including cumulative anthracycline dose) evaluated associations between mean RT dose to each structure and outcomes. Each substructure was individually added to a model with mean whole heart RT dose and the fit was assessed via the likelihood-ratio test to ascertain which substructures improved prediction of cardiac risk beyond whole heart dose.

*Results*:

At 35 years from diagnosis, the cumulative incidence of any cardiac disease was 7.0% (95% CI 6.5 – 7.6). When adding each substructure separately to a model with mean whole heart dose, the addition of mean LAD ($\chi^2$ = 29.1) or LM ($\chi^2$ = 34.6) RT dose significantly improved the risk estimation of any cardiac disease ($p < 0.01$). Among survivors with mean whole heart doses <10 Gy, increasing mean LAD but not mean LM doses significantly increased risk of late cardiac disease. Even among those with a mean heart dose of <5 Gy, mean LAD dose of ≥10 Gy was associated with a more than three-fold increased risk of cardiac disease (**Table 1**).

*Conclusions*:

Even among survivors with low mean heart doses (<5 Gy), mean LAD doses ≥10 Gy increased risk of cardiac disease. Thus, for pediatric RT planning we recommend limiting mean LAD dose to <10 Gy, even when mean heart dose constraints can be achieved.

**Table 1**. Relative rate of grade 3 – 5 cardiac disease in childhood cancer survivors by RT dose to the heart and LAD

| | | **Mean RT dose to LAD** | | | | | |
|---|---|---|---|---|---|---|---|
| | | *No RT* | *0.1 – 4.9 Gy* | *5 – 9.9 Gy* | *10 – 19.9 Gy* | *20 – 29.9 Gy* | *≥30 Gy* |
| **Mean RT dose to the whole heart** | *No RT* | Referent | – | – | – | – | – |
| | *0.1 – 4.9 Gy* | – | 0.9 (0.8 - 1.1) | 1.6 (0.9 - 3.0) | 3.3 (1.8 - 6.0) | * | * |
| | *5 – 9.9 Gy* | – | 0.6 (0.3 - 1.2) | 1.1 (0.6 - 2.0) | 2.3 (1.3 - 4.0) | * | * |
| | *10 – 19.9 Gy* | – | 0.8 (0.5 - 1.5) | 1.4 (1.0 - 2.2) | 3.0 (2.3 - 3.7) | 3.2 (2.3 - 4.6) | 4.7 (2.9 - 7.4) |
| | *20 – 29.9 Gy* | – | * | * | 4.2 (2.9 - 6.0) | 4.6 (3.5 - 6.0) | 6.6 (4.6 - 9.7) |
| | *≥30 Gy* | – | * | * | * | 4.3 (2.7 - 6.7) | 6.2 (4.8 - 8.0) |

* indicates too few survivors for statistical analysis