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Cardiac substructure dosimetry and late cardiac arrhythmia in the Childhood Cancer Survivor Study (CCSS)

Purpose/Objectives:

Increasing radiation (RT) doses to the entire heart increase the risk of cardiac arrhythmias in childhood cancer survivors. However, associations between RT doses to cardiac substructures and the risk of arrhythmia has been inadequately investigated. We evaluated the relationship between RT dose to the heart and risk of arrhythmia and evaluated the contribution of RT dose to the cardiac substructures to this risk.

Materials/Methods:

We determined the cumulative incidence of CTCAE grade 3 – 5 (severe, life-threatening, or fatal) cardiac arrhythmias among 25,481 five-year cancer survivors diagnosed between 1970 to 1999 in the Childhood Cancer Survivor Study (CCSS). Median age was 6.1 years (range 0 – 20 years) at diagnosis and 29.8 years (range 5.6 – 65.9 years) at last follow-up. We reconstructed treatment fields for survivors treated with RT (n = 12,228) on an age-scaled phantom and estimated mean RT dose to the heart, four chambers, four valves, and major coronary arteries (left anterior descending, circumflex, left main, and right coronary (RCA)). Piecewise exponential models evaluated associations between mean RT substructure dose and arrhythmias, adjusted for demographic and treatment-related characteristics, including total anthracycline dose in doxorubicin equivalents. 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 arrhythmia beyond whole heart dose.

Results:

At 35 years from diagnosis, the cumulative incidence of cardiac arrhythmia was 1.4% (95% CI 1.1% - 1.6%). Mean RT doses ≥10 Gy to the whole heart and substructures were associated with an increased risk of arrhythmias (**Table 1**). Low-dose RT (mean RT dose 5.0 – 9.9 Gy) to the RCA was associated with an increased risk of arrhythmia (relative rate (RR) 2.0 95% CI 1.0 – 4.1) compared to survivors who did not receive RT. **Figure 1** shows the associated cumulative incidence by dose levels. Low dose RT to other substructures was not associated with an increased risk of arrhythmia.

Conclusions:

Low dose RT to the RCA increases risk for the development of cardiac arrhythmias. This is intriguing as blood supply to the sinoatrial and atrioventricular nodes commonly arise from the RCA. RT dose to the specific nodal structures was not included in this analysis but should be explored further. These data provide evidence of the importance of cardiac substructure dosimetry in predicting late cardiac disease.

Table 1.

Mean Entire Heart Dose	RR of arrhythmia	95% CI	P value
No RT	Referent		
0.1 – 4.9 Gy	0.9	0.6 – 1.5	0.67
5 – 9.9 Gy	0.3	0.0 – 2.5	0.29
10 – 19.9 Gy	1.9	1.1 – 3.2	0.026
20 – 29.9 Gy	4.8	2.9 – 8.1	<0.001
≥30 Gy	3.6	1.9 – 6.9	<0.001

Figure 1. Cumulative incidence plots of cardiac arrythmia by dose to various cardiac structures