# "Exploring the Role of Mean Cardiac Substructure Dose in Treatment Planning and Cardiac Risk Analyses: A Comparative Study across Treatment Eras"

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**Purpose:**

Recently, the Childhood Cancer Survivor Study (CCSS) reported increased risk of cardiac disease associated with mean radiation therapy (RT) dose to any cardiac substructure (MSD) ≥10Gy, adding to previously reported associations with mean heart dose (MHD) ≥10Gy. We aimed to assess the incorporation of both MSD and MHD into contemporary treatment planning and risk analyses and evaluate the impact of relying solely on MHD-based dose-response models for risk stratification.

**Method:**

We examined the correlation between MHD and 13-specific MSDs (arteries, valves, atria, ventricles, and aorta) among CCSS participants treated with RT between 1970-1999(N=13,081), the CCSS Hodgkin Lymphoma (HL) subset (N=2,599), and contemporarily treated (2000-2021) HL patients (N=29; 48% male/52% female, age at diagnosis 6-20 years). For the CCSS, previously calculated doses were utilized, while for the contemporary patients we retrospectively contoured the same cardiac substructures, calculating MSDs and MHDs. We identified the subset of individuals within each group with MHD<10Gy (considered at low risk based on MHD-dose-response models). Subsequently, within the three subsets, we identified individuals with any MSD≥10Gy (considered at elevated risk based on MSD-dose-response models).

**Results:**

The correlations between MHD and MSDs were 0.96 [Range 0.91-0.99], 0.95 [0.83-0.98], and 0.68 [0.33-0.91] in the entire CCSS cohort, CCSS HL subset, and contemporary HL patients, respectively. Assessing risk exclusively on MHD-dose-response models (MHD<10Gy) could potentially misclassify 3.38% [0.31-6.90], 12.09% [0-33.86], and 35.75% [5.88-88.23] of individuals in each respective group with an elevated risk (MSD≥10Gy ) into a low-risk category.

**Conclusion:**

Given the low correlation between MHD and MSD in contemporary patients, our findings suggest that MSD may play a crucial role in contemporary RT planning and risk estimation. While MHD alone seems adequate for risk classification in historic RT cases, a more nuanced approach suggests that MSD-based analysis is crucial even for survivors treated with historic RT, especially within the subset of Hodgkin's lymphoma patients.