Effect of Heart Anatomy on Radiation Related Cardiac Risk in the Childhood Cancer Survivor Study

Rebecca Howell[1], James Bates[2], Liu Qi[3], Brad Hoppe[2], Choonsik Lee[4], Susan A. Smith[1], Kevin C. Oeffinger[5], Louis S. Constine[6], Wendy M. Leisenring[7], Daniel A. Mulrooney[8], Todd M. Gibson[8], Gregory T. Armstrong[8], Yutaka Yasui[8].
[1]University of Texas at MD Anderson Cancer Center, Radiation Physics, Houston- TX, USA.
[2]University of Florida, Radiation Oncology, Gainsville- FL, USA.
[3]University of Alberta-, Public Health Sciences, Edmonton- AB, Canada.
[4]Radiation Epidemiology Branch, National Cancer Institute, Bethesda- MD, USA.
[5]Duke Universit, Department of Medicine, Durham- NC, USA.
[6]University of Rochester Medical Center, Department of Radiation Oncology, Rochester- NY, USA.
[7]Fred Hutchinson Cancer Research Center, Clinical Research Division, Seattle- WA, USA.
[8]St. Jude Children's Research Hospital, Department of Epidemiology and Cancer Control, Memphis- TN, USA.

Purpose or Objective

We previously estimated rates of severe/disabling, life-threatening, or fatal cardiac disease in 24,214 five-year survivors in the Childhood Cancer Survivor Study (CCSS). At doses ≥10Gy, a linear dose-response relationship was observed between mean heart doses (MHD) and rates of any cardiac disease, coronary artery disease, and heart failure. For each individual, we reconstructed radiation-therapy-(RT)-treatments on age-specific phantoms. MHDs were calculated for a heart model located between thoracic vertebral bodies T5 and T9 (base heart model). Variability in heart anatomy was not considered, and its effect on the dose-response relationship is unknown. This study explored the impact of this variability on the dose response.

Material and Methods

CCSS includes individuals diagnosed in 1970-1999 with median age at diagnosis and attained age of 7.0 (range 0–20.9) and 27.5 (range 5.6–58.9) years, respectively. Those treated with RT (n = 11,668) received conventional RT without Computed-Tomography-(CT)-based planning; heart positions were unknown. To assess the possible range of heart positions, we documented the superior and inferior aspects of hearts from CT scans in a sample of contemporary pediatric RT patients (n=43) and for International Commission on Radiological Protection (ICRP) reference phantoms (ages: 0,1,5,10,15). We classified ten unique heart positions (including that base heart). Nine hearts models were added to our age-specific phantoms. MHDs were calculated for heart models located in ten different positions for each individual. Dose-response relationships were evaluated using weighted piecewise-exponential models adjusting for attained age, sex, age at diagnosis, race, smoking history, year of diagnosis, treatment (alkylating agents, anthracycline, and an interaction between anthracycline and age at diagnosis) where individuals' MHDs were assigned in three ways: (1) base heart; (2) the 10 hearts weighted according to the distribution in the sample group; (3) age-based heart (the heart position of the ICRP phantom of the same age).

Results

Shown in Figure 1(a-b) are scatter plots comparing the MHDs for the base heart model to the alternate dose-assignment methods; corresponding relative rate estimates of the three cardiac-disease rates by MHD are reported in Table I. The estimates are largely consistent between the established heart model using base heart model and the two alternate models. Consistent with our previous findings, here we report that the relative rates of cardiac toxicity increase with MHD ≥ 10 Gy monotonically ($P<0.005$) and agree within 20% regardless of which heart model is used in the analyses.

Conclusion

These data indicate that the heart model used in our previous analysis is robust and representative of the various possible heart positions that may occur for patients in pediatric cohorts. Based on these data, we have confirmed the soundness of our dose response model for cardiac disease.

Mean Heart Dose (Gy)	Any Cardiac Disease Relative Rate (95% CI)		
	Base Heart	**10 Location**	**Age-based**
None	Ref	Ref	Ref
0.1 – 9.9	0.8 (0.6 - 1.0)	0.8 (0.6 - 1.0)	0.8 (0.6 - 1.0)
10 – 19.9	2.0 (1.5 - 2.8)	2.1 (1.6 - 2.8)	2.3 (1.7 - 3.0)
20 – 29.9	2.8 (2.0 - 3.8)	3.1 (2.2 - 4.2)	2.8 (2.0 - 3.8)
> or = 30	6.2 (4.7 - 8.2)	6.2 (4.6 - 8.3)	6.8 (5.1 - 9.2)

Mean Heart Dose (Gy)	Coronary Artery Disease Relative Rate (95% CI)		
	Base Heart	**10 Location**	**Age-based**
None	Ref	Ref	Ref
0.1 – 9.9	1.0 (0.6 -1.5)	1.0 (0.7 - 1.5)	1.0 (0.6 - 1.5)
10 – 19.9	2.8 (1.7 - 4.5)	2.9 (1.8 - 4.5)	3.2 (2.1 - 5.0)
20 – 29.9	3.3 (2.0 - 5.5)	3.7 (2.3 - 6.0)	3.3 (2.0 - 5.5)
> or = 30	7.2 (4.8 - 10.9)	7.1 (4.6 - 10.8)	7.3 (4.8 - 11.1)

Mean Heart Dose (Gy)	Heart Failure Relative Rate (95% CI)		
	Base Heart	**10 Location**	**Age-based**
None	Ref	Ref	Ref
0.1 – 9.9	0.7 (0.5 - 0.9)	0.7 (0.5 - 0.9)	0.7 (0.5 - 0.9)
10 – 19.9	1.6 (1.0 - 2.4)	1.8 (1.2 - 2.6)	1.8 (1.2 - 2.6)
20 – 29.9	2.9 (1.9 - 4.4)	3.4 (2.2 - 5.1)	3.3 (2.2 - 5.0)
> or = 30	6.5 (4.4 - 9.6)	6.2 (4.1 - 9.3)	6.8 (4.5 - 10.3)

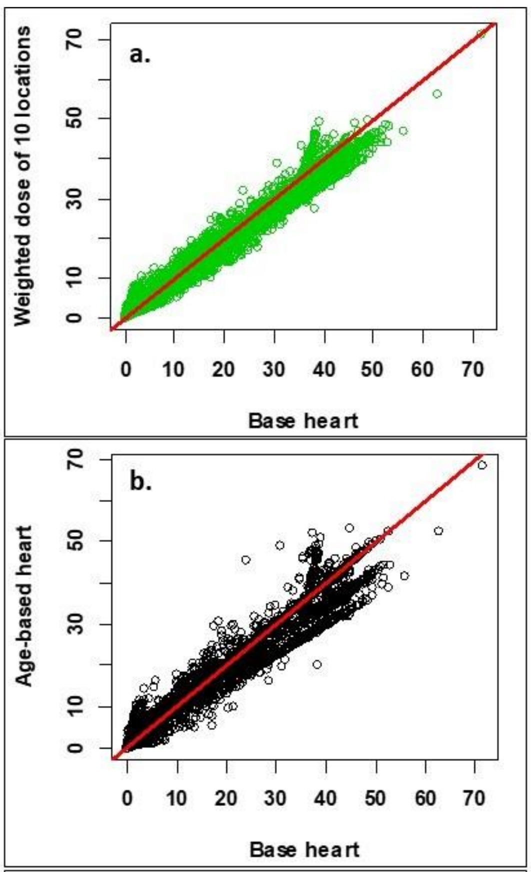

Figure 1: Scatter plots comparing mean heart doses (MHD) for base heart (red line) with MHDs for **a.** 10 hearts weighted based on sample group and **b.** age-based hearts (heart position of ICRP phantom of same age).