Therapy-Related Cardiac Risk in Childhood Cancer Survivors: An Analysis of the Childhood Cancer Survivor Study

James E. Bates, MD¹; Rebecca M. Howell, PhD²; Qi Liu, MSc³; Yutaka Yasui, PhD⁴; Daniel A. Mulrooney, MD⁴; Sugghosh Dhakal, MD⁵; Susan A. Smith, MPH²; Wendy M. Leisenring, ScD⁶; Daniel J. Indelicato, MD¹; Todd M. Gibson, PhD⁴; Gregory T. Armstrong, MD⁴; Kevin C. Oeffinger, MD⁷; and Louis S. Constine, MD⁵

PURPOSE The impacts of radiotherapy dose and exposed cardiac volume, select chemotherapeutic agents, and age at exposure on risk for late-onset cardiac disease in survivors of childhood cancer remain unresolved.

PATIENTS AND METHODS We determined the rates of severe to fatal cardiac disease in 24,214 5-year survivors in the Childhood Cancer Survivor Study diagnosed between 1970 and 1999 at a median age of 7.0 years (range, 0 to 20.9 years), with a median attained age of 27.5 years (range, 5.6 to 58.9 years). Using piecewise exponential models, we evaluated the association between cardiac disease rates and demographic and treatment characteristics.

RESULTS The cumulative incidence of cardiac disease 30 years from diagnosis was 4.8% (95% CI, 4.3 to 5.2). Low to moderate radiotherapy doses (5.0 to 19.9 Gy) to large cardiac volumes ($\geq 50\%$ of heart) were associated with an increased rate of cardiac disease (relative rate, 1.6; 95% CI, 1.1 to 2.3) compared with survivors without cardiac radiotherapy exposure. Similarly, high doses (≥ 20 Gy) to small cardiac volumes (0.1% to 29.9%) were associated with an elevated rate (relative rate, 2.4; 95% CI, 1.4 to 4.2). A dose-response relationship was observed between anthracycline chemotherapy and heart failure with younger children (age ≤ 13 years) at the greatest risk for heart failure after comparable dosing.

CONCLUSION These observations support advances in radiation field design and delivery technology to reduce cardiac dose/volume and should guide future treatment protocols. They also inform clinical practice guidelines for post-therapy surveillance and risk-reducing strategies.

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INTRODUCTION

Cardiac disease is the most common treatment-related, noncancer cause of death among childhood cancer survivors.¹⁻³ Survivors are at risk for a broad spectrum of cardiac conditions, including heart failure (HF), coronary artery disease (CAD), valvular disease, arrhythmia, and pericardial disease.^{2,4}

The dose-response relationships between cardiac disease and both radiotherapy (RT) and anthracycline exposure are well established.^{5,6} The Childhood Cancer Survivor Study (CCSS) reported that mean cardiac RT doses greater than or equal to 15 Gy or cumulative anthracycline doses greater than or equal to 250 mg/m² increase the risk of cardiac disease.⁴ A European investigation of survivors showed that mean cardiac RT doses of 5 to 15 Gy increased the risk of cardiac disease, although the number of events was small.⁷ An international consortium on cardiomyopathy screening guidelines concluded that insufficient evidence exists documenting an increased risk of HF in children who received less than 15 Gy of cardiac RT.⁸ Studies examining the relationship between RT and late cardiac disease have focused on mean cardiac dose.^{4,7} This

oversimplifies a constellation of exposure risks, because mean dose may represent a small portion of the heart receiving a high RT dose, with the remainder of the heart receiving minimal RT dose, or a large portion of the heart receiving a low or moderate RT dose in the absence of any high-dose exposures of the heart. These scenarios may confer differing risk profiles.^{7,9}

Organ-specific vulnerabilities to adverse effects of cancer therapies are influenced by the developmental status of a child as a result of factors such as tissue maturation and capacity for repair.^{10,11} Evidence regarding an association between young age at RT exposure and risk of late-onset cardiac disease is modest. The literature that suggests an association between young age at anthracycline exposure and cardiac disease risk is inconsistent.^{3,6,12,13} Therefore, recent international clinical practice guidelines found the evidence insufficient to recommend enhanced screening among survivors treated at younger ages.⁸

A clear understanding of cardiac disease rates and risk factors after lower-dose cardiac RT is necessary to guide surveillance strategies, drive the use of modern RT treatment techniques (eg, intensity modulation or proton

ASSOCIATED CONTENT

Data Supplement

Podcast by Dr Carver

Author affiliations and support information (if applicable) appear at the end of this article.

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therapy) that reduce mean cardiac RT dose as well as dose to critical substructures (eg, left anterior descending artery), and inform decision making in the design of treatment protocols.¹⁴⁻¹⁷ Currently, data regarding absolute increases in cardiac disease rates, critical for the development of evidence-based screening guidelines and intervention strategies, are sparse.

Our objective was to determine the impact of various cardiac volumes receiving specific RT doses on the rates of serious cardiac conditions in long-term survivors. We also sought to evaluate the association between young age at diagnosis and rate of symptomatic cardiac disease after RT and/or anthracycline chemotherapy among long-term survivors of childhood cancer.

PATIENTS AND METHODS

Study Population

The CCSS is a multi-institutional retrospective cohort study with longitudinal follow-up of survivors of common childhood cancers diagnosed before age 21 years at any of 27 participating institutions across the United States and Canada. Survivors are eligible if they were diagnosed with cancer between January 1, 1970, and December 31, 1999, and survived at least 5 years. The design and methods of the CCSS and participation characteristics have been previously described.¹⁸⁻²⁰ We evaluated a total of 24,355 5-year survivors; 141 developed cardiac disease within 5 years of diagnosis and were excluded, resulting in 24,214 participants. In addition, we evaluated all 5,046 untreated siblings who participated in the CCSS to determine baseline cardiac risk in a comparable population. Institutional review board approval was obtained from each participating institution, and each participant or his or her parent provided informed consent.

Treatment Exposures and Demographics

For each 5-year survivor who received RT, radiation treatment fields were abstracted from his or her RT record and reconstructed on age-specific phantoms (phantoms' ages corresponded to patients' ages at time of RT). Dose to the heart (from direct, adjacent, and/or distant fields) was estimated using previously described methods.²¹ Each dose reconstruction entailed estimating dose to each of 55 points within a three-dimensional grid representing the phantom's heart volume; from those data, we calculated mean dose and percentage of heart volume receiving at least 5 Gy (V5) and 20 Gy (V20). To isolate survivors receiving only low- to moderate-dose RT (meaning no high-dose exposure), we analyzed V5 in survivors with a maximum dose to the heart of less than 20 Gy ($V5_{V20=0\%}$). Details regarding cumulative chemotherapeutic doses were abstracted as previously described.⁴ Doxorubicin-equivalent dose was estimated per previously reported methods.²² Primary diagnosis, cisplatin dose, use of alkylating agent, and sex were also abstracted from medical records. Participants who self-reported ever smoking were defined as having a smoking history. Race and ethnicity were also self-reported. Age at

diagnosis was evaluated, with category of age 0 to 4 years approximating infancy and toddlerhood, that of older than 4 to ≤ 13 years approximating the prepubertal and peripubertal age range, and that of older than 13 years approximating adolescents and young adults.²³

Grade 3 to 5 Cardiac Conditions

Participants reported their age at first occurrence of a wide variety of health outcomes via a series of multi-item, organ system–based questions on the baseline CCSS questionnaire and four subsequent follow-up questionnaires.²⁴ Using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03), chronic health conditions were categorized as mild (grade 1), moderate (grade 2), severe or disabling (grade 3), life threatening (grade 4), or fatal (grade 5).²⁵ When insufficient information was available to distinguish between grades, the lower-severity grade was assigned. Our analysis was restricted to grade 3 to 5 cardiac conditions, including CAD, HF, valvular disease, pericardial disease, and arrhythmias (Data Supplement). Patients who developed any one of those conditions were marked as having any cardiac disease. We also separately analyzed CAD and HF risks.

Statistical Analysis

Demographic and treatment characteristics were examined in all 5-year survivors. To determine cardiac disease incidence, a time-to-event analysis starting at 5 years from diagnosis was conducted for three groups of cardiac disease: any cardiac disease, CAD, and HF. Death, second malignant neoplasm, and recurrence were treated as competing risk events. Patients were censored at the time of the last completed questionnaire. Cumulative incidence curves of the three outcomes were estimated and compared according to demographic and treatment characteristics using Gray's K-sample test.²⁶

To assess the dose-response relationships for the incidence rate of each outcome, piecewise exponential models adjusting for attained age, sex, race, smoking history, and year of diagnosis were used. Modifications of treatment effects by age at diagnosis and other treatment modalities were further evaluated using these models. Adjusted relative rates (RRs), 95% CIs, and *P* values were estimated using standard large-sample inference methods. All tests were two sided, and *P* < .05 indicated statistical significance. Absolute excess risk (AER) calculations were performed comparing the survivor population with the sibling population. SAS (version 9.4; SAS Institute, Cary, NC) and R software (version 3.4.0; R Foundation, Vienna, Austria) were used for statistical analyses.

RESULTS

Characteristics and Overall Outcomes

Table 1 lists the demographic characteristics of the 24,214 survivors. Most were between the ages of 4 and 13 years at

diagnosis. Median attained age of the cohort was 27.5 years (range, 5.6 to 58.9 years). Median follow-up was 20.3 years (range, 5.0 to 39.3 years). [Table 2](#) lists the treatment exposures of the survivors; approximately half of the survivors received RT (51.6%) or an anthracycline (47.4%); 25.4% were exposed to both. There were 658 survivors with at

least one grade 3 to 5 cardiac condition, including 371 with HF, 304 with CAD, 96 with arrhythmia, 70 with valvular disease, and 28 with pericardial disease (Data Supplement); 158 survivors had two or more different grade 3 to 5 cardiac conditions. The cumulative incidence of having at least one grade 3 to 5 cardiac condition at 30 years was

TABLE 1. Demographic Characteristics of Survivors of Childhood Cancer

Characteristic	All Survivors (N = 24,214)	Any RT to Heart (n = 11,960)	Any Anthracycline (n = 10,457)	No RT to Heart and No Anthracycline (n = 4,889)
Attained age, years				
Median	27.5	29.9	26.2	25.6
Range	5.6-58.9	5.6-58.3	5.6-55.0	6.1-58.9
Follow-up, years				
Median	20.3	21.8	18.4	20.6
Range	5.0-39.3	5.0-38.9	5.0-38.5	5.5-39.2
Age at diagnosis, years				
≤ 4	7,799 (34.1)	3,323 (28.7)	3,050 (32.8)	2,246 (46.7)
> 4 to ≤ 13	10,113 (42.7)	5,239 (44.4)	4,243 (42.6)	1,863 (38.7)
> 13	6,302 (23.2)	3,398 (26.9)	3,164 (24.6)	780 (14.5)
Year of diagnosis				
1970-1979	6,578 (27.2)	4,188 (35.0)	1,735 (16.6)	888 (16.4)
1980-1989	9,728 (40.2)	4,802 (40.2)	4,270 (40.8)	2,080 (41.1)
1990-1999	7,908 (32.6)	2,970 (24.8)	4,452 (42.6)	1,921 (42.4)
Sex				
Male	12,955 (53.6)	6,425 (54.1)	5,653 (54.1)	2,442 (50.3)
Female	11,259 (46.4)	5,535 (45.9)	4,804 (45.9)	2,447 (49.7)
Any history of smoking*				
Yes	6,901 (29.0)	3,211 (27.6)	2,950 (28.5)	1,476 (30.5)
No	16,555 (71.0)	8,321 (72.4)	7,103 (71.5)	3,324 (69.5)
Race/ethnicity				
White non-Hispanic	19,803 (81.0)	10,109 (83.9)	8,363 (79.1)	4,033 (81.5)
Black non-Hispanic	1,516 (6.4)	634 (5.5)	711 (6.9)	239 (4.8)
Hispanic	1,805 (8.0)	741 (6.4)	864 (8.8)	400 (9.0)
Other	1,090 (4.7)	476 (4.1)	519 (5.1)	217 (4.7)
Cancer diagnosis				
Leukemia	7,282 (38.4)	3,512 (33.7)	4,090 (51.5)	1,116 (30.2)
CNS tumors	4,313 (15.7)	2,239 (17.6)	31 (0.2)	1,600 (29.6)
Hodgkin lymphoma	2,985 (10.9)	2,290 (18.0)	1,262 (9.6)	60 (1.1)
Non-Hodgkin lymphoma	1,976 (7.2)	761 (6.0)	1,280 (9.8)	216 (4.0)
Wilms tumor	2,141 (7.8)	1,053 (8.3)	884 (6.7)	718 (13.3)
Neuroblastoma	1,837 (6.7)	602 (4.7)	694 (5.3)	656 (12.1)
Soft tissue sarcoma	1,693 (6.2)	957 (7.5)	624 (4.8)	367 (6.8)
Bone cancer	1,987 (7.2)	546 (4.3)	1,592 (12.1)	156 (2.9)

NOTE. Data are presented as No. (%) unless otherwise noted. Analyses, including reported percentages, were weighted to account for undersampling of acute lymphoblastic leukemia survivors in the latter recruitment era (1987 to 1999), with a weight of 1.21 for those age 0 or 11 to 20 years at diagnosis and a weight of 3.63 for those age 1 to 10 years.

Abbreviation: RT, radiotherapy.

*Numbers and percentages of these variables are based on available data.

4.8% (95% CI, 4.3% to 5.2%); the overall AER compared with the sibling population was 1.28 events per 1,000 person-years.

Demographic Effects

Cumulative incidence and adjusted incidence rates for developing any grade 3 to 5 cardiac disease did not differ by sex (Table 3; Data Supplement); however, compared with female survivors, male survivors were more likely to develop CAD (RR, 1.3; 95% CI, 1.0 to 1.7) and less likely to develop

HF (RR, 0.7; 95% CI, 0.5 to 0.9). Non-Hispanic black survivors were more likely to develop any cardiac disease than non-Hispanic white survivors (RR, 1.7, 95% CI, 1.2 to 2.4); this was observed for both CAD (RR, 2.5; 95% CI, 1.5 to 4.2) and HF (RR, 2.0; 95% CI, 1.3 to 3.1).

RT Effects

A dose-response relationship between mean cardiac RT dose and any cardiac disease, CAD, and HF was observed at mean doses to the heart greater than or equal to 10 Gy

TABLE 2. Treatment Exposures of Survivors of Childhood Cancer

Variable	All Survivors (N = 24,214)	Any RT to Heart (n = 11,960)	Any Anthracycline (n = 10,457)	No RT to Heart and No Anthracycline (n = 4,889)
Mean cardiac RT dose, Gy*				
None	9,569 (48.4)	NA	4,639 (51.3)	NA
> 0-9.9	7,399 (32.6)	7,399 (63.2)	3,599 (33.4)	NA
10-19.9	1,912 (8.3)	1,912 (16.0)	982 (8.7)	NA
20-29.9	1,364 (5.5)	1,364 (10.7)	568 (4.5)	NA
≥ 30	1,285 (5.2)	1,285 (10.1)	262 (2.1)	NA
Volume of heart receiving ≥ 5 Gy when maximum heart dose is < 20 Gy (V5 _{V20=0%}), %*				
No cardiac irradiation	9,569 (56.3)	NA	4,639 (56.4)	NA
0†	6,507 (33.5)	6,506 (76.6)	3,122 (32.1)	NA
0.1-49.9	450 (2.1)	450 (4.9)	204 (1.8)	NA
≥ 50	1,540 (8.1)	1,540 (18.5)	957 (9.7)	NA
Volume of heart receiving ≥ 20 Gy V20, %*				
No cardiac irradiation	9,569 (48.4)	NA	4,639 (51.3)	NA
0‡	8,497 (37.6)	8,496 (72.8)	4,283 (39.7)	NA
0.1-29.9	283 (1.2)	283 (2.2)	147 (1.2)	NA
30-79.9	707 (2.9)	707 (5.5)	230 (1.8)	NA
≥ 80	2,475 (10.0)	2,474 (19.4)	751 (6.0)	NA
Cumulative anthracycline dose, mg/m ² *				
None	11,615 (49.6)	6,324 (52.4)	NA	NA
1-249	6,305 (35.6)	3,135 (30.8)	6,305 (70.6)	NA
≥ 250	3,455 (14.8)	1,900 (16.8)	3,455 (29.4)	NA
Cumulative cisplatin dose, mg/m ² *				
None	20,132 (92.6)	10,758 (92.5)	9,165 (90.9)	4,799 (98.5)
1-299	558 (2.2)	321 (2.6)	322 (2.5)	30 (0.6)
≥ 300	1,300 (5.2)	619 (5.0)	862 (6.6)	52 (1.0)
Received alkylating agents*				
Yes	11,929 (54.8)	6,871 (59.7)	8,030 (75.5)	979 (18.4)
No	10,094 (45.2)	4,824 (40.3)	2,421 (24.5)	3,901 (81.6)

NOTE. Data are presented as No. (%). Analyses, including reported percentages, were weighted to account for undersampling of acute lymphoblastic leukemia survivors in the latter recruitment era (1987 to 1999), with a weight of 1.21 for those age 0 or 11 to 20 years at diagnosis and a weight of 3.63 for those age 1 to 10 years.

Abbreviations: NA, not applicable; RT, radiotherapy.

*Numbers and percentages of these variables are based on available data.

†Indicates maximum RT dose to heart of 0.1 to 4.9 Gy.

‡Indicates maximum RT dose to heart of 0.1 to 19.9 Gy.

TABLE 3. Thirty-Year Cumulative Incidence and RRs for Grade 3 to 5 Cardiac Disease Among 5-Year Survivors of Childhood Cancer by Demographic and Treatment Factors

Variable	Any Cardiac Disease			CAD			HF		
	30-Year Cumulative Incidence (%) (95% CI)	Adjusted RR (95% CI)	P	30-Year Cumulative Incidence (%) (95% CI)	Adjusted RR (95% CI)	P	30-Year Cumulative Incidence (%) (95% CI)	Adjusted RR (95% CI)	P
Sex									
Male	4.5 (3.9 to 5.1)	0.9 (0.8 to 1.1)	.32	2.4 (2.0 to 2.9)	1.3 (1.0 to 1.7)	.03	2.1 (1.7 to 2.5)	0.7 (0.5 to 0.9)	.002
Female	5.1 (4.4 to 5.8)	Ref	Ref	2.3 (1.8 to 2.9)	Ref	Ref	3.0 (2.5 to 3.6)	Ref	Ref
Race/ethnicity									
White non-Hispanic	4.6 (4.1 to 5.1)	Ref	Ref	2.3 (2.0 to 2.7)	Ref	Ref	2.4 (2.0 to 2.7)	Ref	Ref
Black non-Hispanic	8.4 (5.0 to 11.7)	1.7 (1.2 to 2.4)	.004	3.9 (2.0 to 5.7)	2.5 (1.5 to 4.2)	< .001	5.4 (2.5 to 8.3)	2.0 (1.3 to 3.1)	.001
Hispanic	4.1 (2.4 to 5.7)	1.0 (0.7 to 1.5)	.91	2.2 (0.9 to 3.6)	1.4 (0.8 to 2.4)	.24	2.0 (0.9 to 3.1)	0.7 (0.4 to 1.3)	.26
Other	5.2 (2.8 to 7.7)	1.1 (0.7 to 1.8)	.69	1.6 (0.2 to 3.1)	0.3 (0.1 to 1.3)	.11	4.4 (2.0 to 6.8)	1.8 (1.1 to 2.9)	.03
History of smoking									
Yes	5.5 (4.6 to 6.4)	1.1 (0.9 to 1.3)	.40	3.0 (2.3 to 3.6)	1.3 (1.0 to 1.6)	.08	2.6 (2.0 to 3.3)	1.0 (0.7 to 1.3)	.77
No	4.4 (3.8 to 4.9)	Ref	Ref	2.1 (1.7 to 2.5)	Ref	Ref	2.4 (2.0 to 2.8)	Ref	Ref
Mean cardiac radiotherapy dose, Gy									
None	3.4 (2.6 to 4.2)	Ref	Ref	1.0 (0.6 to 1.5)	Ref	Ref	2.5 (1.8 to 3.2)	Ref	Ref
0.1-9.9	2.6 (2.0 to 3.1)	0.8 (0.6 to 1.1)	.12	1.0 (0.7 to 1.4)	1.0 (0.6 to 1.5)	.88	1.4 (1.0 to 1.7)	0.7 (0.5 to 1.0)	.05
10-19.9	5.8 (4.2 to 7.4)	2.2 (1.6 to 2.9)	< .001	3.2 (1.9 to 4.5)	3.0 (1.9 to 4.8)	< .001	2.6 (1.6 to 3.6)	1.7 (1.1 to 2.7)	.01
20-29.9	7.7 (5.2 to 10.2)	2.8 (2.0 to 3.8)	< .001	3.7 (1.9 to 5.4)	3.2 (1.9 to 5.4)	< .001	4.7 (2.7 to 6.7)	2.9 (1.9 to 4.6)	< .001
≥ 30	17.3 (14.5 to 20.0)	6.4 (4.8 to 8.5)	< .001	11.9 (9.5 to 14.3)	7.5 (4.9 to 11.4)	< .001	6.9 (5.2 to 8.7)	6.7 (4.6 to 9.9)	< .001
Cumulative anthracycline dose, mg/m ²									
None	3.7 (3.1 to 4.2)	Ref	Ref	2.5 (2.1 to 3.0)	Ref	Ref	1.2 (0.9 to 1.5)	Ref	Ref
1-249	4.3 (3.2 to 5.4)	1.7 (1.1 to 2.5)	.01	2.0 (1.3 to 2.8)	1.4 (0.8 to 2.3)	.26	1.9 (1.3 to 2.5)	2.9 (1.6 to 5.3)	< .001
≥ 250	8.4 (6.9 to 9.9)	2.4 (1.7 to 3.5)	< .001	1.9 (1.2 to 2.6)	0.7 (0.3 to 1.3)	.22	7.2 (5.7 to 8.6)	6.5 (4.0 to 10.6)	< .001
Alkylating agents									
No	3.6 (3.0 to 4.2)	Ref	Ref	1.9 (1.4 to 2.3)	Ref	Ref	1.8 (1.4 to 2.2)	Ref	Ref
Yes	5.9 (5.1 to 6.7)	1.2 (1.0 to 1.4)	.13	2.9 (2.3 to 3.4)	1.2 (0.9 to 1.6)	.11	3.1 (2.6 to 3.7)	1.1 (0.8 to 1.4)	.53
Anthracycline dose, 0 mg/m ² ; age at diagnosis, years									
≤ 4	1.2 (0.9 to 1.6)	1.1 (0.6 to 1.8)	.80	0.3 (0.1 to 0.6)	0.8 (0.4 to 1.8)	.63	0.8 (0.5 to 1.1)	1.3 (0.6 to 2.9)	.49
> 4 to ≤ 13	3.9 (2.5 to 5.3)	1.1 (0.8 to 1.5)	.57	1.4 (0.4 to 2.3)	1.2 (0.8 to 1.8)	.34	3.1 (1.7 to 4.5)	1.3 (0.8 to 2.2)	.34
> 13	5.5 (3.6 to 7.3)	Ref	Ref	1.5 (0.6 to 2.4)	Ref	Ref	3.9 (2.3 to 5.5)	Ref	Ref

(continued on following page)

TABLE 3. Thirty-Year Cumulative Incidence and RRs for Grade 3 to 5 Cardiac Disease Among 5-Year Survivors of Childhood Cancer by Demographic and Treatment Factors (continued)

Variable	Any Cardiac Disease			CAD			HF		
	30-Year Cumulative Incidence (%) (95% CI)	Adjusted RR (95% CI)	P	30-Year Cumulative Incidence (%) (95% CI)	Adjusted RR (95% CI)	P	30-Year Cumulative Incidence (%) (95% CI)	Adjusted RR (95% CI)	P
Anthracycline dose, 1-249 mg/m ² ; age at diagnosis, years									
≤ 4	2.7 (1.8 to 3.6)	2.1 (1.3 to 3.5)	.005	0.7 (0.2 to 1.2)	2.6 (1.2 to 5.7)	.02	1.6 (0.9 to 2.3)	2.1 (1.0 to 4.2)	.04
> 4 to ≤ 13	2.6 (1.8 to 3.3)	1.4 (0.9 to 2.2)	.13	1.4 (0.8 to 2.0)	1.2 (0.7 to 2.4)	.50	1.2 (0.7 to 1.6)	1.5 (0.8 to 2.8)	.17
> 13	2.2 (1.1 to 3.4)	Ref		0.7 (0.1 to 1.3)	Ref		1.4 (0.5 to 2.4)	Ref	
Anthracycline dose ≥ 250 mg/m ² ; age at diagnosis, years									
≤ 4	4.7 (2.3 to 7.1)	4.0 (2.5 to 6.4)	< .001	2.2 (0.6 to 3.9)	4.3 (1.4 to 12.9)	.01	2.7 (0.8 to 4.5)	4.6 (2.7 to 7.9)	< .001
> 4 to ≤ 13	3.8 (2.1 to 5.5)	2.4 (1.7 to 3.5)	< .001	1.4 (0.2 to 2.7)	3.3 (1.5 to 7.2)	.003	2.8 (1.4 to 4.3)	2.5 (1.7 to 3.8)	< .001
> 13	12.7 (6.9 to 18.5)	Ref		9.2 (3.8 to 14.7)	Ref		2.1 (0.4 to 3.8)	Ref	

NOTE. Estimates presented are adjusted for all factors included in this table, including interaction between anthracycline dose and age at diagnosis, attained age as cubic splines, and year at diagnosis and cumulative cisplatin dose.

Abbreviations: CAD, coronary artery disease; HF, heart failure; Ref, referent; RR, relative rate.

FIG 1. Cumulative incidence, based on (A-C) mean heart dose, (D-F) volume of heart (%) receiving radiotherapy (RT) greater than or equal to 20 Gy, and (G-I) volume of heart (%) receiving RT greater than or equal to 5 Gy when maximum heart dose is less than 20 Gy. (J-L) Cumulative anthracycline dose. (*) 0% maximum radiation dose to the heart = 0.1 to 19.9 Gy. (†) 0% maximum radiation dose to the heart = 0.1 to 4.9 Gy.

(Table 3; Figs 1A to 1C). High doses (≥ 20 Gy) to small cardiac volumes (0.1% to 29.9%) were associated with an elevated rate (RR, 2.4; 95% CI, 1.4 to 4.2) compared with unexposed survivors, primarily because of an increased rate of HF (Figs 1D to 1F). Likewise, low to moderate doses (5.0 to 19.9 Gy) to large cardiac volumes ($\geq 50\%$ of the heart) were associated with an increased rate of cardiac disease (RR, 1.6; 95% CI, 1.1 to 2.3), compared with unexposed survivors (Table 4; Figs 1G to 1I). This was primarily because of an increased rate of CAD. Importantly, we did not observe a clinically significant association between age at diagnosis and cardiac irradiation on the rate of cardiac disease. The Data Supplement shows the number of patients in each of the mean heart RT dose and volumetric categories. The AERs by mean RT dose and volume and by cumulative anthracycline dose are listed in Table 5.

Anthracycline Effects

We observed a dose-response relationship between anthracycline exposure and any cardiac disease (0.1 to < 250 mg/m²: RR, 1.7; 95% CI, 1.1 to 2.5; ≥ 250 mg/m²: RR, 2.4; 95% CI, 2.7 to 3.5; Table 3; Figs 1J to 1L), primarily because of an increased rate of HF. Among survivors who received a low to intermediate cumulative anthracycline dose, children age 0 to 4 years had an increased rate compared with older children (1 to 249 mg/m²; age 0 to 4

$v > 13$ years: RR, 2.1; 95% CI, 1.3 to 3.5; Table 3). Among those receiving high-dose anthracycline chemotherapy (≥ 250 mg/m²), children age 0 to 4 years (RR, 4.0; 95% CI, 2.5 to 6.4) and older than 4 to ≤ 13 years at diagnosis (RR, 2.4; 95% CI, 1.7 to 3.5) had an increased risk of any cardiac disease relative to those age older than 13 years at diagnosis. The association of anthracycline dose with rate of cardiac disease was not modified by cardiac RT dose (data not shown).

DISCUSSION

In this study of a large, geographically diverse, well-characterized cohort of childhood cancer survivors with longitudinal follow-up, we report two novel findings with valuable clinical implications. Both low- to moderate-dose RT to a large volume of the heart and high-dose RT to a small volume of the heart are associated with a substantially elevated risk of cardiac disease. In addition, we confirm that young age at anthracycline exposure confers greater risk for cardiac disease, a finding that strengthens the evidence for including this risk in future screening guidelines.

Our data confirm the findings of prior studies that have established the relationship between mean cardiac RT dose and risk for late cardiac disease.^{4,7} Our findings substantially broaden these observations with what is, to

TABLE 4. Thirty-Year Cumulative Incidence and RRs for Grade 3 to 5 Cardiac Disease Among 5-Year Survivors of Childhood Cancer by Percentage Volume of Heart Receiving Specific RT Doses

Volume of Heart Receiving RT (%)	Any Cardiac Disease				CAD				HF			
	30-Year Cumulative Incidence (%)		Adjusted RR (95% CI)		30-Year Cumulative Incidence (%)		Adjusted RR (95% CI)		30-Year Cumulative Incidence (%)		Adjusted RR (95% CI)	
	(95% CI)		(95% CI)	P	(95% CI)		(95% CI)	P	(95% CI)		(95% CI)	P
Volume of heart receiving 5 Gy when V20 = 0% (V5V20=0%), %												
No RT*	3.4 (2.6 to 4.1)		Ref	Ref	1.0 (0.6 to 1.5)		Ref	Ref	2.5 (1.8 to 3.2)		Ref	Ref
0†	2.6 (2.0 to 3.1)		0.8 (0.6 to 1.0)	.11	1.1 (0.7 to 1.5)		1.0 (0.7 to 1.6)	.86	1.3 (0.9 to 1.6)		0.6 (0.5 to 0.9)	.02
0.1-49.9	2.1 (0.3 to 3.8)		0.7 (0.3 to 1.5)	.39	0.0 (0.0 to 0.0)		0.3 (0.0 to 2.4)	.26	1.8 (0.2 to 3.5)		0.7 (0.3 to 1.8)	.49
≥ 50	4.0 (2.6 to 5.3)		1.6 (1.1 to 2.3)	.02	2.4 (1.2 to 3.5)		2.3 (1.3 to 4.0)	.003	1.8 (1.0 to 2.7)		1.3 (0.8 to 2.2)	.29
Volume of heart receiving > 20 Gy (V20), %												
No RT*	3.4 (2.6 to 4.1)		Ref	Ref	1.0 (0.6 to 1.5)		Ref	Ref	2.5 (1.8 to 3.2)		Ref	Ref
0†	2.8 (2.3 to 3.3)		0.9 (0.7 to 1.1)	.41	1.2 (0.9 to 1.6)		1.2 (0.8 to 1.8)	.39	1.4 (1.1 to 1.8)		0.8 (0.6 to 1.0)	.08
0.1-29.9	6.4 (2.9 to 9.9)		2.4 (1.4 to 4.2)	.003	1.9 (0.0 to 3.8)		2.1 (0.7 to 5.9)	.16	3.7 (1.1 to 6.4)		2.3 (1.1 to 4.8)	.02
30-79.9	8.6 (5.7 to 11.5)		3.3 (2.3 to 4.8)	< .001	4.7 (2.4 to 7.1)		3.7 (2.1 to 6.5)	< .001	4.6 (2.7 to 6.6)		3.4 (2.1 to 5.6)	< .001
≥ 80	13.7 (11.5 to 15.8)		4.5 (3.5 to 5.7)	< .001	8.9 (7.1 to 10.7)		5.6 (3.8 to 8.2)	< .001	5.8 (4.4 to 7.3)		4.5 (3.2 to 6.2)	< .001

NOTE. The two sections in this table (ie, volume ≥ 5 Gy and volume ≥ 20 Gy) come from separate models that are exclusive of each other and adjusted for attained age as cubic splines, age at diagnosis, sex, race, history of smoking, year of diagnosis, alkylating agents, anthracycline dose, interaction between anthracycline dose and age at diagnosis, and cisplatin dose.

Abbreviations: CAD, coronary artery disease; HF, heart failure; Ref, referent; RR, relative rate; RT, radiotherapy.

*No RT to the heart.

†Indicates maximum RT dose to heart of 0.1 to 4.9 Gy.

‡Indicates maximum RT dose to heart of 0.1 to 19.9 Gy.

TABLE 5. AER of Grade 3 to 5 Cardiac Disease in 5-Year Survivors of Childhood Cancer Compared With Siblings of Childhood Cancer Survivors

Variable	Anthracycline Dose (mg/m ²)								
	Any Cardiac Disease (events per 1,000 person-years)			CAD (events per 1,000 person-years)			HF (events per 1,000 person-years)		
	0	1-249	≥ 250	0	1-249	≥ 250	0	1-249	≥ 250
Mean cardiac RT dose, Gy									
None	0.09	0.40	3.08	0.14	0.20	0.54	0.04	0.47	2.81
>0-9.9	0.17	0.67	2.01	0.14	0.39	0.36	0.05	0.34	1.85
10-19.9	1.16	2.26	4.38	1.06	1.29	0.41	0.21	1.20	4.05
20-29.9	1.67	1.79	8.10	1.21	0.23	2.57	0.62	1.57	5.39
≥ 30	6.82	10.3	13.8	4.95	6.32	5.33	2.43	4.96	10.5
Volume of heart receiving 5 Gy when maximum heart dose is < 20 Gy (V5 _{V20=0%}), %									
No cardiac RT	0.09	0.40	3.08	0.14	0.20	0.54	0.04	0.47	2.81
0*	0.18	0.52	2.01	0.16	0.41	0.37	0.05	0.19	1.87
0.1-49.9	0.31	0.94	0.99	0.07	0.00	0.00	0.07	1.08	1.15
≥ 50	0.52	1.54	4.13	0.74	1.06	0.49	0.00	0.78	3.69
Volume of heart receiving ≥ 20 Gy (V20), %									
0 and dose 0 Gy	0.09	0.40	3.08	0.14	0.20	0.54	0.04	0.47	2.81
0†	0.24	0.77	2.22	0.23	0.54	0.36	0.05	0.36	2.05
0.1-29.9	0.80	6.25	4.05	0.22	1.98	0.97	0.27	4.20	3.13
30-79.9	2.08	5.02	8.25	1.69	0.46	2.59	0.60	4.12	7.50
≥ 80	4.80	3.68	9.65	3.48	1.90	3.14	1.73	2.10	6.60

Abbreviations: AER, absolute excess risk; CAD, coronary artery disease; HF, heart failure; RT, radiotherapy.

*Indicates maximum RT dose to heart of 0.1 to 4.9 Gy.

†Indicates maximum RT dose to heart of 0.1 to 19.9 Gy.

our knowledge, the largest assessment (pediatric or adult) of the relationship between the volume of the heart irradiated and the risk of late-onset cardiac disease. Importantly, survivors whose hearts were exposed to low- to moderate-dose RT (5 to 19 Gy) to a large volume of the heart (≥ 50%) had a 1.6-fold increased risk of cardiac disease compared with those who received no RT to the heart. Exposing any volume of the heart to RT doses of ≥ 20 Gy confers an increased risk of cardiac disease, affirming the toxic potential of these doses even to small cardiac volumes. These dose-volume relationships were not substantially influenced by age at diagnosis, suggesting these relationships may also exist in young adults treated for cancer.

Our findings regarding risks of RT-related late cardiac disease must be considered in the context of evolving RT technology. Contemporary RT volumes and doses for diseases such as Hodgkin lymphoma are smaller than those in earlier eras, and novel RT delivery techniques such as intensity-modulated radiotherapy (IMRT) or proton therapy significantly reduce both mean heart dose and volume of the heart exposed to even low doses, and the potential exists to minimize dose to critical substructures

(eg, coronary arteries).¹⁴⁻¹⁷ These reductions may result in exposures below what we have reported to be associated with cardiac risk.^{14,16} Certain modern techniques such as IMRT, although increasing conformality, may also increase the volume of the heart receiving low-dose RT for patients treated with mediastinal RT. Our study cohort was treated before the widespread adoption of IMRT; however, the finding that low- to moderate-dose RT (5 to 19 Gy) to a large volume of the heart (≥ 50%) increases cardiac disease risk should be strongly considered in risk assessment of children otherwise thought to be at low risk for cardiac disease. Continuous evaluation of the relationship between RT and heart disease as cohorts of survivors treated with these modern techniques mature will be important to determine the consistency of the reported risk factors with contemporary techniques and individualize cardiac risk assessments. Highly conformal RT techniques were uncommon during the years our patients were treated (1970 to 1999) and unlikely to have influenced outcomes, because rates of HF and CAD were consistent across these decades as previously reported.²⁷ Our data provide strong support for continued efforts to minimize both the heart RT dose and exposed volume to avoid late cardiac disease.

Moreover, generations of current survivors were treated with older, more damaging techniques, and our findings provide additional evidence to guide risk-based screening for cardiac disease.

Anthracyclines are cardiotoxic across the age spectrum, with the youngest patients at the time of exposure at highest risk. This is a consequence of cardiomyocyte damage leading to HF.²⁸ We reaffirm this relationship at both low and high cumulative doses. The youngest children (age ≤ 4 years at diagnosis) are exceptionally vulnerable to anthracycline-mediated toxicity, with cardiac disease rates twice those of their teenage counterparts at low doses (0.1 to 250 mg/m²) and four times those of their teenage counterparts at higher doses (≥ 250 mg/m²). Age at diagnosis must be considered in evaluating the cardiac risk profile of long-term survivors. Of note, most of our study cohort was treated before the use of dexrazoxane as a cardioprotectant, which may alter the dose-response relationship.²⁹

Demographic variables also play a role in risk for cardiac disease in survivors of childhood cancer. We confirm that female survivors are at greater risk of HF, likely related to their increased propensity for anthracycline-related HF.³⁰ We also show that male survivors are at a slightly increased risk of CAD. The exact explanation for this is unclear; however, it may be related to an increased incidence of CAD in males in the general population.^{31,32} We observed an increased rate of cardiac disease among non-Hispanic black survivors. This has been previously reported within the CCSS; however, this association was attenuated in a model including socioeconomic status variables that we did not consider in our investigation.³³ This putative relationship should be studied further in additional cohorts of childhood cancer survivors.

Our findings inform current international guidelines for screening and early detection of cardiac disease in survivors of childhood cancer. We contribute significant information regarding the AER of cardiac disease, crucial for the development of said guidelines. In addition, there is no current guidance for survivors exposed to less than 15 Gy mean cardiac RT doses because of a paucity of data.⁸ Our analysis fills this important gap. Mean doses greater than or equal to 10 Gy were associated with increased overall risk of cardiac disease, CAD, and HF, suggesting that surveillance and risk-reducing strategies should be considered for any survivor receiving a mean cardiac dose of greater than or equal to 10 Gy. These data additionally support continued

surveillance of survivors who may have received high cardiac doses to small volumes of the heart from RT fields targeted to nearby structures. Current cardiomyopathy screening guidelines do not include age at anthracycline exposure because of insufficient information.⁸ Our data suggest that the youngest children are at the greatest risk of anthracycline-related cardiac disease, even at low or intermediate cumulative doses. Increased screening frequency among children receiving anthracyclines at age ≤ 13 years should be considered.

There are several strengths of this study, including large sample size, geographic and racial heterogeneity, extensive range of treatment exposures, and longitudinal follow-up. The primary limitation is that grade 3 to 4 cardiac outcomes were self-reported; validation of cardiac outcomes was previously attempted and found unfeasible.⁴ By limiting our analysis to Common Terminology Criteria for Adverse Events grade 3 to 5 events representing clinically symptomatic disease verified by requiring medical intervention, this potential for bias may have been mitigated. However, by omitting grade 1 to 2 events, we likely underrepresent true cardiac risk in this population. In addition, this cohort has a median age of just 27.5 years, when cardiac disease is uncommon in the general population. It is likely that with additional follow-up, the incidence of cardiac disease will continue to rise among survivors, given the increased prevalence in the general population. Because specific cardiac RT exposures were not detailed in the historical RT records, they were reconstructed from medical records and modeled in age-appropriate phantoms rather than on individual patient anatomy; this approach can only approximate the actual doses received. Beyond this, the relevance of RT exposure to specific cardiac structures could not be determined.

Our report substantially expands the understanding of late cardiac disease in survivors of childhood cancer. Cardiac disease risk varies by mean cardiac RT dose and volume of heart receiving both low- to moderate-dose and high-dose RT. Anthracycline exposure also increases this risk. The youngest children are at the greatest risk of toxicity from any anthracycline exposure, emphasizing the vulnerability of this population. However, age does not substantially modify the RT volume-response relationship for cardiac toxicity, suggesting that these observations may also apply to other age groups. These findings will further inform and guide surveillance protocol design, clinical trial structure, and methods of RT delivery for pediatric patients with cancer.

AFFILIATIONS

¹University of Florida, Gainesville, FL

²MD Anderson Cancer Center, Houston, TX

³University of Alberta, Edmonton, Alberta, Canada

⁴St Jude Children's Research Hospital, Memphis, TN

⁵University of Rochester Medical Center, Rochester, NY

⁶Fred Hutchinson Cancer Research Center, Seattle, WA

⁷Duke University, Durham, NC

CORRESPONDING AUTHOR

Louis S. Constine, MD, University of Rochester Medical Center, 601 Elmwood Ave, Box 647, Rochester, NY 14642; e-mail: louis_constine@urmc.rochester.edu.

EQUAL CONTRIBUTION

K.C.O. and L.S.C. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHOR CONTRIBUTIONS

Conception and design: James E. Bates, Daniel A. Mulrooney, Sugghosh Dhakal, Wendy M. Leisenring, Gregory T. Armstrong, Kevin C. Oeffinger, Louis S. Constine

Financial support: Gregory T. Armstrong

Administrative support: Gregory T. Armstrong, Kevin C. Oeffinger

Provision of study material or patients: Gregory T. Armstrong

Collection and assembly of data: Rebecca M. Howell, Sugghosh Dhakal, Susan A. Smith, Wendy M. Leisenring, Gregory T. Armstrong

Data analysis and interpretation: James E. Bates, Qi Liu, Yutaka Yasui, Daniel A. Mulrooney, Daniel J. Indelicato, Todd M. Gibson, Gregory T. Armstrong, Kevin C. Oeffinger, Louis S. Constine

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Therapy-Related Cardiac Risk in Childhood Cancer Survivors: An Analysis of the Childhood Cancer Survivor Study

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Susan A. Smith

Honoraria: Memorial Sloan Kettering Cancer Center

Travel, Accommodations, Expenses: Memorial Sloan Kettering Cancer Center

Daniel J. Indelicato

Travel, Accommodations, Expenses: IBA

Louis S. Constine

Honoraria: UpToDate, Springer, Lippincott

Travel, Accommodations, Expenses: Particle Therapy Cooperative Group of North America

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