Cardiovascular Concerns in AYA and Adult Survivors of Childhood Cancer

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Principal Investigator, Childhood Cancer Survivor Study

Department of Epidemiology and Cancer Control
Disclosure

- Grail: Consultant, Circulating Tumor DNA Profiling
Average Years of Life Lost Per Person Dying of Cancer
All Races, Both Sexes, 2013

- Childhood Ages (0-14) 35.1
- Testis 20.5
- Cervix Uteri 22.1
- Hodgkin Lymphoma 21.8
- Brain & ONS 19.1
- Breast (Female) 17.1
- Ovary 17.4
- Corpus & Uterus, NOS 17.3
- Oral Cavity & Pharynx 17.1
- Liver & BID 16.4
- Melanoma of the Skin 16.8
- Stomach 16.4
- Esophagus 16.1
- Kidney & Renal Pelvis 15.8
- Leukemia 15.6
- Colon & Rectum 15.4
- Lung & Bronchus 15.2
- Pancreas 15.1
- Non-Hodgkin Lymphoma 14.0
- Myeloma 13.6
- Urinary Bladder 11.4
- Prostate 9.9

Source: US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention and 2011 Life Tables.
Natural History of Cardiotoxicity: Differing Paradigms

- **Cancer**
- **CHF**
- **CAD**

**Hodgkin Lymphoma**
- Increasing risk

**Quality Years Lost**

**Problem for Research**
- Rare disease
- Long latency period
Goals

• Risk and risk factors for cardiovascular disease
• The well-appearing survivor…surveillance/screening
• Modifiable cardiovascular risk factors
• The good news
What large cohort data tells us about risk and risk factors for cardiotoxicity?
Survivorship Statistics

- >85% of children with a malignancy will achieve five-year survival
- In 2018, estimated 483,000 survivors of childhood cancer in the U.S.
- As of 2020, estimated 500,000 survivors
Cause-Specific Mortality Among Aging Survivors

Standardized Mortality Ratio

SMN = 15.2
Cardiac = 7.0

Clinical Heart Failure
CTCAE Grades 3-5


Cumulative Incidence (%)

At 45 Years
11.8%
6.8%
5.0%
0.3%

Age (years)

RT + anthracycline
Anthracycline alone
RT alone
No RT or anthracycline
Sibling

P < .001
Coronary Artery Disease
CTCAE Grades 3-5

At 45 Years
9.0%
1.0%
0.3%

Risk for CHF after Anthracyclines is DOSE DEPENDENT

Fig 1. Dose-response relationship between cumulative anthracycline exposure and risk of cardiomyopathy. Patients with no exposure to anthracyclines served as the referent group. Magnitude of risk is expressed as odds ratio, which was obtained using conditional logistic regression adjusting for age at diagnosis, sex, and chest radiation.


There is NO safe dose of anthracycline!
High-Dose RT/Small Volume Increases Risk

<table>
<thead>
<tr>
<th>Volume $20_{\text{Gy}}$</th>
<th>30-Year Cumulative Incidence</th>
<th>Adjusted Rate Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT</td>
<td>3.4%</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>0%</td>
<td>2.8%</td>
<td>0.9 (0.7 – 1.1)</td>
<td>0.41</td>
</tr>
<tr>
<td>0.1 – 29.9%</td>
<td>6.4%</td>
<td>2.4 (1.4 – 4.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>30 – 79.9%</td>
<td>8.6%</td>
<td>3.3 (2.3 – 4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥80%</td>
<td>13.7%</td>
<td>4.5 (3.5 – 5.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean heart dose

- None
- 0.1 to < 10 Gy
- 10 to < 20 Gy
- 20 to < 30 Gy
- ≥ 30 Gy

Low-Dose RT/Large Volume Increases Risk

<table>
<thead>
<tr>
<th>Volume of heart receiving ≥ 5 Gy when max heart dose &lt;20 Gy</th>
<th>Cumulative Incidence (%)</th>
<th>Any Cardiac Disease</th>
<th>Coronary Artery Disease</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT to Heart</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>3.4%</td>
<td>Ref</td>
<td>0.8 (0.6 – 1.0)</td>
<td>0.11</td>
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<tr>
<td>0.1% – 49.9%</td>
<td>2.6%</td>
<td>0.7 (0.3 – 1.5)</td>
<td>0.39</td>
<td></td>
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<tr>
<td>≥50%</td>
<td>4.0%</td>
<td>1.6 (1.1 – 2.3)</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

There is likely NO safe dose of chest-directed RT!
Risk for CHF INCREASES as Survivors Age


Health Disparities in Survivor Outcomes

Genetic Variants Associated with Racial Disparity in Therapy-Related Cardiomyopathy

- African-American (AA) survivors at increased risk for CTCAE grade 3-4 cardiomyopathy (OR 2.47, 95% CI 1.33-4.59)
- Locus at 1p13.2 (P = 2.8 x 10^{-8}) associated with increased risk for Grade 3-4 cardiomyopathy (OR 5.43, 95% CI 2.20-13.43)
- Among African-Americans the \textit{PHTF1} promoter region was hypomethylated
- \textit{PHTF1} upregulated in hi-PSC derived cardiomyocytes from patients with Doxorubicin-induced cardiomyopathy (DIC)
Cumulative Burden of Conditions Hodgkin Lymphoma Survivors


Cumulative Incidence (Grades 1-5)

Cumulative Burden (Grades 1-5)
Example of Need for Survivor-Specific Risk Prediction Models

40-year-old male Hodgkin survivor exposed to anthracyclines and chest radiation.
BP 130/85, HDL 60, LDL 90, no smoking history, no current medication use.

American College of Cardiology atherosclerotic cardiovascular disease (ASCVD) risk calculator
10-year risk = 0.5%
http://tools.acc.org/ascvd-risk-estimator-plus

Chow/Childhood Cancer Survivor Study Ischemic Heart Disease risk calculator
10-year risk 9.7%
Chow, et al J Clin Oncol 2017
CCSS Cardiovascular Risk Calculator

This risk assessment tool predicts risk of heart failure, ischemic heart disease, and stroke by age 50 among survivors of childhood cancer. It uses information from the CCSS papers, "Individual prediction of heart failure among childhood cancer survivors" (Chow et al., ...) and "Prediction of ischemic heart disease and stroke among childhood cancer survivors" (Chow et al., ...), which created clinically useful models with readily available demographic and cancer treatment information. These models were designed specifically for patients who have recently completed cancer treatment (5 years from cancer diagnosis). These models have been validated in separate groups of childhood cancer survivors: Emma Children’s Hospital and Academic Medical Center (Amsterdam, the Netherlands), the St. Jude Lifetime Cohort Study, and the National Wilms Tumor Study.

Depending on what level of treatment information is available, we created three different prediction models:

- Simple (if anthracycline, alkylator, platinum-agent chemotherapy, and radiation exposures to the brain, neck, and chest are known, but not the doses)
- Standard (if anthracycline and chest radiation doses are known)
- Standard+heart (if anthracycline dose and heart-specific radiation dosimetry are known)

To determine one’s risk of cardiovascular disease, please enter the information below (All fields are Required):

Gender?
- Male
- Female

Patient’s age at diagnosis?
- < 5
- 5 - 9
- 10 - 14
- ≥ 15

Were any anthracyclines used?
- No
- Yes, cumulative dose known
- Yes, but cumulative dose unknown
- Unknown if anthracyclines used
The Well Appearing Survivor

Surveillance/Screening
Case

July 1984:

**History:** 12 yo female with ~6 wks R knee pain, edema, difficulty ambulating after trauma

**Diagnostic Imaging:** large mass distal R femur; chest neg, bone scan only uptake in femur

**Biopsy of R femur:** Osteosarcoma

**Treatment:** PG8107 protocol – completed 8/1985
- Right AKA
- Chemotherapy: anthracycline 380mg/m$^2$
  - HD MTX, bleomycin, cisplatin, dactinomycin, cyclophosphamide (5700mg/m$^2$)
Case

January 2009  SJLIFE Evaluation (Age 37)
- GERD – on PPI
- Iron deficiency anemia – iron injections
- Chronic Hepatits C – not requiring treatment to date
- Hypertension, dyslipidemia

Cardiac Evaluation
- Echocardiogram  ?
Long-Term Follow-Up Guidelines
for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 5.0 - October 2018

Website: www.survivorshipguidelines.org
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Pediatric Guideline Design

Evidence linking late effects with therapeutic exposures

Screening recommendations based on expert clinical experience

Allows identification of high-risk categories

Matches magnitude of risk with intensity of screening

Evidence-Based Guidelines for Childhood Cancer Survivors: A Hybrid Model
Screening Recommendations for Cardiac Function: COG Guidelines

- **Periodic evaluation**
  - Detailed history yearly
  - EKG for evaluation of QT interval at baseline
  - 2D ECHO for evaluation of systolic function at baseline, then periodically based on:
    - History of chest radiation
    - Cumulative anthracycline dose
Monitoring Survivors for Cardiomyopathy

Survivorshipguidelines.org

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<tr>
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<th>Radiation Dose**</th>
<th>Recommended Frequency</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>&lt; 15 Gy or none</td>
<td>No screening</td>
</tr>
<tr>
<td>≥ 15 - &lt; 35 Gy</td>
<td></td>
<td>Every 5 years</td>
</tr>
<tr>
<td>≥ 35 Gy</td>
<td></td>
<td>Every 2 years</td>
</tr>
<tr>
<td>&lt; 250 mg/m²</td>
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*Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33.

**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76.
Yield of Cardiac Screening

Percent yield of CV screening = \( \frac{\text{# of outcomes diagnosed at SJLIFE assessment}}{\text{# at risk – outcomes diagnosed before SJLIFE}} \)

- Cardiomyopathy: 4.7%, 72 diagnosed at SJLIFE, 46 diagnosed before SJLIFE
- Coronary Artery Disease: 2.2%, 40 diagnosed at SJLIFE, 29 diagnosed before SJLIFE
- Valve Disorder: 24.8%, 414 diagnosed at SJLIFE, 74 diagnosed before SJLIFE
- Conduction Disorders: 1.4%, 25 diagnosed at SJLIFE, 53 diagnosed before SJLIFE

Comprehensive Echocardiographic Detection of Treatment-related Cardiac Dysfunction

Armstrong GT, et al, JACC  2015
Cardiac Remodeling

![Cardiac Remodeling Diagram]

- **Concentric Remodeling**
- **Concentric Hypertrophy**
- **Normal Geometry**
- **Eccentric Hypertrophy**

Relative Wall Thickness

- > 0.42
- ≤ 0.42

Left Ventricular Mass Index (g/m²)

- ≤ 95 (♀)
- ≤ 115 (♂)
- > 95 (♀)
- > 115 (♂)
Cardiac Remodeling

Remodeling Phenotypes
- Normal Geometry
- Eccentric hypertrophy
- Concentric hypertrophy
- Concentric remodeling

Below normal
- Normal
- Mildly abnormal
- Moderately abnormal
- Severly abnormal

Left Ventricular Mass Categories
- All Participants
- Non-Exposed
- Anthracycline Only
- Chest Radiation Only
- Anthracycline and Chest Radiation
- Control

Prevalence (%)
# Cardiopulmonary Exercise Testing Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Exposed Survivors (N=824)</th>
<th>Unexposed Survivors (N=436)</th>
<th>Community Controls (N=285)</th>
<th>Exposed vs. Controls (p)</th>
<th>Unexposed vs. Controls (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO(_2) Peak (ml/kg/min)</td>
<td>25.7 ± 8.6</td>
<td>26.8 ± 2.4</td>
<td>32.7 ± 7.8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VO(_2) Peak (% predicted)</td>
<td>78 ± 22</td>
<td>82 ± 21</td>
<td>98 ± 20</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise Intolerance (peak VO(_2) uptake &lt;85% predicted)</td>
<td>63.8%</td>
<td>55.7%</td>
<td>26.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Harmonizing Cardiomyopathy Surveillance Recommendations After Treatment of Childhood Cancer

Coronary Artery Disease Surveillance Guidelines: International Guideline Harmonization Group

Coronary artery disease surveillance among childhood, adolescent and young adult cancer survivors: A systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Elvira C. van Dalen a, Renée L. Mulder a, Eugene Suh b, Matthew J. Ehrhardt c, Gregory J. Aune d, Edit Bardi e, Bradley J. Benson g, Jutta Bergler-Klein g, Ming H. Chen f, Eva Frey f, Ulrike Hennewig i, Liane Lockwood g, Ulla Martinsson j, Monica Muraca m, Helena van der Pal k, Chris Plummer n, Katrin Scheinemann o, Christina Schindera p, Emily S. Tonorezos i, W. Hamish Wallace g, Louis S. Constine i, Roderick Skinner i, Melissa M. Hudson o, Leon M. C.M. Kremer o, Gill Levitt s, Daniel A. Mulrooney o, s

Van Dalen et. al., European Journal of Cancer, 2021
Modifiable Cardiovascular Risk Factors

Longitudinal management of risk across the lifespan
Modifiable Risk Factors & Major Cardiac Events

Evaluate relative contribution to development of CHF

- Longitudinal evaluation
- 10,724 survivors, CCSS
- Is risk simply additive?

- Hypertension potentiates anthracycline-associated risk for CHF

- Multiple traditional CV risk factors increase risk

Chest RT and Multiple Risk Factors Including Hypertension

Coronary Artery Disease

- Multiple RFs alone: RR=7.9
- Chest RT alone: RR=5.0
- Chest RT + Multiple RFs: RR=39.8

p<0.001

Congestive Heart Failure

- Multiple RFs alone: RR=5.2
- Chest RT alone: RR=3.7
- Chest RT + Multiple RFs: RR=26.3

p=0.002

Blood Pressure Status in Adult Survivors of Childhood Cancer

Cumulative Prevalence of Hypertension by Attained Age in SJLIFE

- Standardized Prevalence Ratio = 2.6 (1.7-4.7)
- Expected based on age, sex, race/ethnicity and BMI-specific rates from NHANES

Gibson et al, Cancer Epidemiol Biomarkers Prev, 2017
So, can you give us some good news?

Historical reductions in therapeutic exposure and changes in risk patterns for cardiac outcomes
## Treatment-related Cause Late Mortality: 15 Years from Diagnosis

<table>
<thead>
<tr>
<th>Era</th>
<th>Treatment-related Cause</th>
<th>Subsequent Neoplasms</th>
<th>Cardiac</th>
<th>Pulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970-74</td>
<td>3.5%</td>
<td>1.8%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>1975-79</td>
<td>2.9%</td>
<td>1.5%</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td>1980-84</td>
<td>2.7%</td>
<td>1.3%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>1985-89</td>
<td>2.2%</td>
<td>1.3%</td>
<td>0.1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>1990-94</td>
<td>2.1%</td>
<td>1.0%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Armstrong et al, NEJM 2016
Dexrazoxane

- Limited data regarding cardio-protective effect in pediatrics.
  - May improve SF, but only statistically significant in girls.
- The ongoing ALTE11C2 study seeks to prospectively assess cardiac function in patients previously treated with dexrazoxane on COG legacy trials.

Chow, E. et al. Cancer in press

Lipshultz, S. et al. Lancet Onc 2010
Exercise

- Higher activity is associated with decreased mortality.

Scott, J. et al. *JAMA Onc* 2018
Conclusions

- Survivors are at HIGH risk for poor cardiac outcomes at a relatively young age
  - No safe dose of Anthracyclines
  - No safe dose of chest RT
  - Risk increases with age and is always > the general population risk

- Survivors need personalized, risk-based care
  - Principle of early detection, though no evidence (yet) for improved major outcomes
  - Reduced EF is a late finding in the natural history, early markers are needed
  - Individual risk calculator exists

- Traditional CVRFs increase risk in a near multiplicative fashion!!!
  - Importance of prevention, heart healthy lifestyle, and adequate treatment

- More recent survivors may have lower risk
The Childhood Cancer Survivor Study is an NCI-funded resource to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence.

Investigators interested in potential uses of this resource are encouraged to visit:

www.stjude.org/ccss
Survival Following Onset of CHF is **VERY BAD**

NEW Screening Recommendations for Cardiac Function: 2018 COG Guidelines

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<td></td>
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*Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33.

**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76.
### Mitoxantrone to Doxorubicin Equivalency

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Participants, No.</th>
<th>HR (95% CI)</th>
<th>Ratio (95% CI)</th>
<th>Linear Dose-Response Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Clinical Cardiomyopathy</td>
<td>Dose Information</td>
<td>Mean</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>65</td>
<td>4328</td>
<td>1.4 (0.9-2.1)</td>
<td>1.8 (1.2-2.6)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td></td>
<td>2.8 (1.7-4.5)</td>
<td>4.6 (3.3-6.4)</td>
</tr>
<tr>
<td>Mitoxantronec</td>
<td>19</td>
<td>261</td>
<td>4.2 (1.8-9.9)</td>
<td>4.2 (1.6-11.4)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td></td>
<td></td>
<td>1.5 (1.0-2.3)</td>
<td>4.4 (3.2-6.0)</td>
</tr>
<tr>
<td>Mitoxantrone to doxorubicin ratio</td>
<td>2.8</td>
<td>1.0</td>
<td>4.2</td>
<td>10.9 (6.2-19.1)</td>
</tr>
</tbody>
</table>

- CCSS
- Dutch Childhood Oncology Group
- National Wilms Tumor Study Group

(n=20,367)

Feijen, EA. et al. JAMA Oncol 2019
NT-proBNP Associated with Future Grade 2-5 Cardiac Events Among Survivors with normal EF

MACE=major adverse cardiac event (MI, cardiomyopathy, vascular disease or stroke). Adjusted for age at diagnosis, attained age, sex, race, BMI and baseline cardiovascular risk factors (hypertension, diabetes, dyslipidemia).

Limited to 535 survivors exposed to cardiotoxic therapy without grade 3-4 cardiomyopathy and with normal LVEF at baseline.

Dixon S et. al., Cancer, 2020
# International Guidelines

<table>
<thead>
<tr>
<th>Risk</th>
<th>Anthracycline (mg/m²)</th>
<th>Chest RT (Gy)</th>
<th>Anthracycline (mg/m²) + chest RT (Gy)</th>
<th>Surveillance</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>≥ 250</td>
<td>≥ 35</td>
<td>≥ 100 and ≥ 15</td>
<td>Yes</td>
<td>5-year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consider more frequent</td>
</tr>
<tr>
<td>Moderate</td>
<td>100 to &lt; 250</td>
<td>15 to &lt; 35</td>
<td>–</td>
<td>Maybe</td>
<td>5-year</td>
</tr>
<tr>
<td>Low</td>
<td>&gt; 0 to &lt; 100</td>
<td>&gt; 0 to &lt; 15</td>
<td>–</td>
<td>Maybe</td>
<td>5-year</td>
</tr>
</tbody>
</table>

- **Strong recommendation, high-quality evidence**
- **Moderate recommendation, moderate-quality evidence**
- **Moderate recommendation, weak-quality evidence**

Ehrhardt, MJ. et al *J Clin Oncol* 2020
## International Guidelines

**Cost Effectiveness Model-supported Recommendations**

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<td></td>
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<td>Maybe</td>
<td>5-year</td>
<td>No</td>
<td>No screening</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Legend</strong></th>
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<th></th>
<th></th>
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<tr>
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<td>Strong recommendation, high-quality evidence</td>
<td>Moderate recommendation, moderate-quality evidence</td>
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Ehrhardt, MJ. et al *J Clin Oncol* 2020