Cardiotoxicity in Aging Survivors of Childhood Cancer

Gregory T. Armstrong
Assistant Member

Department of Epidemiology and Cancer Control
Survivorship Statistics*

- In 2005, estimated 328,600 childhood cancer survivors in the U.S.
- Estimated 366,000 by 2010
- 1 in 680 is a childhood cancer survivor (ages 20 to 50 years)

* Source: NCI Office of Cancer Survivorship, Mariotto et al, CEBP, 2009
Cause-specific Mortality Among Aging Survivors

Armstrong GT, et al, JCO, 2009
Cumulative Incidence of Chronic Health Conditions: Grades 3-5

Armstrong GT, ASCO 2012
Cumulative Incidence Grade 3–5 by Organ Systems

- New Malignancy
- Hearing
- Renal
- Cardiac
- Vision
- Respiratory

Armstrong GT, ASCO 2012
## Chronic Health Conditions Grading

Common Terminology Criteria for Adverse Events v4.03 (self report)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Descriptor</th>
<th>Examples: Cardiac Conditions</th>
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<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>Arrhythmia, no medications</td>
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<td>Myocardial infarct, Cath/CABG, Valve replacement, Cardiac transplant</td>
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<td>Cardiac death</td>
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Cardiac Outcomes Among Long-term Survivors of Childhood Cancer

- Compared to siblings, adult survivors had a 5.9-fold increased risk of congestive heart failure, 5-fold risk of myocardial infarction, and 6.3-fold risk of valvular disease.

- Risk of cardiac event was significantly associated with anthracycline exposure >250 mg/m² and >15 Gy cardiac radiation.

- Risk continues to increase 30 years after diagnosis.

Key Questions

• Impact of traditional cardiovascular risk factors?

• Novel identification of cardiopulmonary late effects with aging?

• Efficacy of current screening guidelines?

• Novel screening endpoints?
Key Questions

• Impact of traditional cardiovascular risk factors?

• Novel identification of cardiopulmonary late effects with aging?

• Efficacy of current screening guidelines?

• Novel screening endpoints?
Funded in 1994
Retrospective Cohort, diagnosed 1970-1986
26 Contributing Centers
5-Year Survival
Leukemia, Lymphoma, CNS, Bone, Wilms, NBL, Soft-tissue sarcoma
Detailed Treatment Data, Wide Range of Outcomes
190+ Publications since 2001

20,720 Eligible
Lost (n=3017)
17,703 Contacted
Refusal (n=3189)
14,372 Participants

Cohort Expansion: 1987-1999
n=16,721
<table>
<thead>
<tr>
<th>Study Population at Baseline (N=10,724)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>5101 (48)</td>
</tr>
<tr>
<td>Male</td>
<td>5623 (52)</td>
</tr>
<tr>
<td>Chest directed RT exposure</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>2532 (26)</td>
</tr>
<tr>
<td>None</td>
<td>7058 (74)</td>
</tr>
<tr>
<td>Anthracycline exposure</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5926 (63)</td>
</tr>
<tr>
<td>1–299 mg/m²</td>
<td>1831 (19)</td>
</tr>
<tr>
<td>≥300 mg/m²</td>
<td>1630 (18)</td>
</tr>
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### Chronic Health Conditions Grading

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Cumulative Incidence at age 45: Cardiovascular Events (grade 3–5)

- **Coronary Artery Disease**
  - RT
  - No RT
  - Siblings

- **Congestive Heart Failure**
  - RT + Anthracycline
  - Anthracycline
  - RT
  - No RT + Anthracycline
  - Siblings

- **Valve Abnormality**
  - RT
  - No RT
  - Siblings

- **Arrhythmia**
  - RT
  - No RT
  - Siblings
Cardiovascular Disease Risk Factors:
- BMI ≥30 (obesity)
- medical Rx for hypertension, dyslipidemia, diabetes

Cardiovascular Risk Factor Cluster:
- Any three or more risk factors

Data Collection:
- Baseline & three follow-up studies
Cardiovascular Risk Factors: Prevalence

**Hypertension**
- Survivor: 39%
- Sibling: 28%

**Dyslipidemia**
- Survivor: 28%
- Sibling: 18%

**Diabetes**
- Survivor: 9%
- Sibling: 5%

**BMI ≥ 30 kg/m³**
- Sibling: 36%
- Survivor: 21%
Cardiovascular Risk Factor Cluster

Prevalence of Multiple Cardiac Risk Factors

- Survivor (9.2%)
- Sibling (8.2%)

Age Group:
- <30 years
- 30–39 years
- 40–49 years
- ≥50 years
# Chest RT and Multiple Risk Factors

<table>
<thead>
<tr>
<th>Referent</th>
<th>RT</th>
<th>CVRFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referent</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RT Effect</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CVRFC Effect</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Combined Effect</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Armstrong et al, Manuscript under review
Chest RT and Multiple Risk Factors

Coronary Artery Disease

- CVRFC alone: RR=5.9
- Chest RT alone: RR=4.3
- Chest RT + CVRFC: RR=32.2

p<0.001

Congestive Heart Failure

- CVRFC alone: RR=4.0
- Chest RT alone: RR=3.7
- Chest RT + CVRFC: RR=19.0

p=0.002
An NCI-funded Resource

Anthracycline and Multiple Risk Factors

Congestive Heart Failure

- CVRFC alone: RR=6.7
- Chest RT alone: RR=4.9
- Chest RT + CVRFC: RR=17.7

p=0.05

Armstrong et al, Manuscript under review
## Cardiac Mortality: Risk Factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>2.2</td>
<td>0.8-6.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.5</td>
<td>3.2-9.7</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.7</td>
<td>0.7-3.8</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.2</td>
<td>0.6-2.3</td>
</tr>
<tr>
<td>Multiple Risk Factors</td>
<td>2.4</td>
<td>1.2-4.9</td>
</tr>
</tbody>
</table>

Adjusting for: sex, race/ethnicity, education, household income

Armstrong et al, Manuscript under review
Conclusions & Limitations

• Conclusions
  – Modifiable cardiovascular risk factors potentiate risk after chest-directed RT
  – Hypertension, most significant independent risk factor

• Limitation
  – Survey-based cardiac outcomes, no confirmation of cardiac events
Key Questions

- Impact of traditional cardiovascular risk factors?
- Novel identification of cardiopulmonary late effects with aging?
- Efficacy of current screening guidelines?
- Novel screening endpoints?
Pulmonary Hypertension

- **Progressive** condition, characterized by ↑Pulmonary Artery (PA) pressures leading to RV failure

**Etiology**
- “Idiopathic" or “Primary”
- Drugs & toxins (cocaine, amphetamines)
- Left-sided heart failure
- Lung disease (interstitial, COPD, sleep apnea)

**Population & Methods**
- 498 survivors, Chest RT/Anthracycline
- Median age 37 years of age (20-59 year)
- TR jet velocity >2.8 m/sec
## Prevalence of ↑TR Jet Velocity

<table>
<thead>
<tr>
<th>TR Jet Velocity</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population (N = 498)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.8 m/sec</td>
<td>423</td>
<td>85.0</td>
</tr>
<tr>
<td>&gt;2.8-3.4 m/sec</td>
<td>69</td>
<td>13.9</td>
</tr>
<tr>
<td>&gt;3.4 m/sec</td>
<td>6</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Survivors with any chest-directed RT (N= 234)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.8 m/sec</td>
<td>175</td>
<td>74.8</td>
</tr>
<tr>
<td>&gt;2.8-3.4 m/sec</td>
<td>54</td>
<td>23.1</td>
</tr>
<tr>
<td>&gt;3.4 m/sec</td>
<td>5</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Survivors with chest-directed RT ≥30Gy (N = 107)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.8 m/sec</td>
<td>74</td>
<td>69.2</td>
</tr>
<tr>
<td>&gt;2.8-3.4 m/sec</td>
<td>28</td>
<td>26.2</td>
</tr>
<tr>
<td>&gt;3.4 m/sec</td>
<td>5</td>
<td>4.7</td>
</tr>
</tbody>
</table>
Prevalence of ↑ TR Jet Velocity

Armstrong GT et al, in press, JCO

<table>
<thead>
<tr>
<th>Group</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6.1%</td>
</tr>
<tr>
<td>1–19.9 Gy</td>
<td>16.2%</td>
</tr>
<tr>
<td>20–29.9 Gy</td>
<td>22.2%</td>
</tr>
<tr>
<td>≥30 Gy</td>
<td>30.8%</td>
</tr>
</tbody>
</table>

% >2.8 m/s
## Treatment Associated Risk Factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT</strong></td>
<td></td>
</tr>
<tr>
<td>≥30Gy</td>
<td>4.53 (1.77-11.64)</td>
</tr>
<tr>
<td>20-29.9Gy</td>
<td>3.46 (1.59-7.54)</td>
</tr>
<tr>
<td>1-19.9Gy</td>
<td>2.09 (0.63-6.96)</td>
</tr>
<tr>
<td>None</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
</tr>
<tr>
<td>≥40kg/m2</td>
<td>3.89 (1.46-10.39)</td>
</tr>
<tr>
<td>&lt;25kg/m2</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Anthracycline</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.77 (0.35-1.65)</td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Adjusting for: sex, race/ethnicity, education and current age

Armstrong GT *et al*, in press, *JCO*
Etiology of ↑TR Jet Velocity

- Chest directed RT for treatment of primary cancer
  - Lung Irradiation
  - Heart Irradiation

  + Increased pulmonary arteriolar pressure
  + Pulmonary hypertension
  + Increased pulmonary venous pressure
## Etiology of ↑TR Jet Velocity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Atrial Pressure</strong> <em>(E/E’)</em></td>
<td></td>
</tr>
<tr>
<td>Moderate/Severe <em>(≥12)</em></td>
<td>4.55 (2.04 - 10.13)</td>
</tr>
<tr>
<td>Mild <em>(9 to 13)</em></td>
<td>0.44 (0.17 - 1.11)</td>
</tr>
<tr>
<td>Normal <em>(&lt;9)</em></td>
<td>1.00 (1.00 - 1.00)</td>
</tr>
<tr>
<td><strong>Pulmonary Function</strong> <em>(FVC,FEV₁,TLC, DLCOcorr)</em></td>
<td>Abnormal <em>(&lt;60%)</em></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
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Adjusting for: sex, race/ethnicity, education, obesity and current age

Armstrong GT et al, in press, *JCO*
Etiology of ↑ TR Jet Velocity

- Lung Irradiation
  - Pulmonary vascular and alveolar injury
  - Pulmonary fibrosis with increased vascular resistance
    - Increased pulmonary ateriolar pressure
      - Pulmonary hypertension
        - Increased pulmonary venous pressure
          - ↑ Left atrial pressure (E/E')

- Heart Irradiation
- Chest directed RT for treatment of primary cancer
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic function</td>
<td></td>
</tr>
<tr>
<td>EF &lt;50%</td>
<td>2.05 (0.94-4.45)</td>
</tr>
<tr>
<td>EF ≥50%</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiac injury mechanisms</td>
<td></td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>5.85 (2.05-16.74)</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>2.38 (0.80-7.07)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.97 (0.51-1.85)</td>
</tr>
</tbody>
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Adjusting for: sex, race/ethnicity, education, obesity and current age

Armstrong GT et al, in press, JCO
Etiology of Pulmonary Hypertension

- Lung Irradiation
  - Pulmonary vascular and alveolar injury
  - Pulmonary fibrosis with increased vascular resistance
  - Increased pulmonary arteriolar pressure
  - Pulmonary hypertension
  - Increased pulmonary venous pressure

- Chest directed RT for treatment of primary cancer

- Heart Irradiation
  - Aortic valve regurgitation
  - Myocardial fibrosis
  - Coronary artery disease
  - Hypertension
  - ↑ Left atrial pressure (E/E')
14 participants completing <300 meters
  - None had amputation or limb sparing procedure
  - 12 could not complete the first 50 meters due to dyspnea, tachypnea, or ↑BP
Conclusions & Limitations

- Conclusions
  - TRJ velocity/chest RT dose-response relationship
  - Associated with reduced functional capacity
  - Mediated through cardiac > pulmonary injury (?)

- Limitations
  - Need for cath. confirmation → future RO1
    - Pulmonary venous vs. pulmonary arterial
  - Assessment of sleep disordered breathing
  - Improved echo assessment:
    - Right heart failure
    - Diastolic contribution
Key Questions

• Impact of traditional cardiovascular risk factors?

• Novel identification of cardiopulmonary late effects with aging?

• Efficacy of current screening guidelines?

• Novel screening endpoints?
Long-Term Follow-Up Guidelines
for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 3.0 – October 2008

CureSearch
Children’s Oncology Group

www.survivorshipguidelines.org

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Screening Recommendations: 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:
    • Age at treatment
    • History of chest radiation
    • Cumulative anthracycline dose
Long-term Medical Care

Nathan PC et al, JCO 2009
Prevalence of Echo Screening

Nathan PC et al, JCO 2009
Screening Adult Survivors of Childhood Cancer for Cardiomyopathy

Comparison of Echocardiography and Cardiac MRI
- 114 adult survivors
- 25% with >350 mg/m2 anthracycline, 1/3 with Chest RT
- Median age: 39 years (range 22-53)

Findings:
- Mean EF: 2D echo overestimates by 5%
- 2D echo had ↓sensitivity and ↑false negative rate
- At an EF cutoff of 50%, 11% of population misclassified as normal
- 3D echo improves sensitivity

Conclusions:
- In this high-risk population, consider lower threshold for referral to subspecialty cardiology care

Armstrong GT et al, JCO 2012
Key Questions

• Impact of traditional cardiovascular risk factors?

• Novel identification of cardiopulmonary late effects with aging?

• Efficacy of current screening guidelines?

• Novel screening endpoints?
Primary Aim- Identify whether myocardial strain provides improved detection of functional cardiotoxicity (VO2 max) compared to EF

Hypothesis- Strain will be more closely associated with VO2 max than EF

Population-
- 810 survivors exposed to anthracyclines and/or chest-RT
- 480 non-exposed survivor controls

Potential Confounders-
- Pulmonary function
- Neuromuscular strength
- Anemia
• The Childhood Cancer Survivor Study is an NCI-funded resource (U24 CA55727) 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:

  http://ccss.stjude.org
Exposed to Chest RT and/or Anthracycline Chemotherapy and Eligible for Evaluation of Pulmonary Hypertension (N=737)

- Declined Participation (N=67)
  - Passive Non-participant (N=57)
  - Interested, Evaluation to be Scheduled (N=58)

Agreed to Participate (n=555)

Clinically Evaluated for SJLIFE (n=519)

- Survey Only, No SJCRH Visit (N=31)
  - Agreed, Evaluation Scheduled (N=5)

Echocardiogram performed (n=505)

- Echo not performed (n=14)

Tricuspid Regurgitant Jet Velocity Evaluable (n=498)