Cardiovascular Oncology in 2017:
Radiation induced CV Disease
Survivorship

John Groarke MBBCh MSc MPH
Instructor of Medicine, Harvard Medical School,
Cardio-Oncology Program/ Advanced Heart Disease Section
Brigham and Womens Hospital/Dana Farber Cancer Institute
Boston, MA
Disclosures

• Amgen Pharmaceuticals (Grant Support)
• Linda Joy Pollin Women’s Heart Center Innovation Award
Talk Outline

• **Part I: Radiation induced cardiovascular injury**
  – Risk factors
  – Practice guidelines pertaining to surveillance and testing
  – Cardiac surgery outcomes in pts with RIHD
  – Radiation-induced carotid disease and management
  – Refinements in radiation protocols to reduce cardiac exposure

• **Part II: Survivorship**
  – Guidelines for survivors of childhood and adult cancers
  – Adverse cardiometabolic profiles of cancer survivors
  – Prevalence and significance of impaired exercise capacity
RADIATION INDUCED CARDIOVASCULAR INJURY
CV Complications of Radiation Therapy

• ~50% of cancer patients receive RT\textsuperscript{1}
• CV complications originally described in 1960s\textsuperscript{2}

![Figure 1](image_url)

**Radiation-Induced Cardiovascular Injury**

- Risk factors:
  - Higher radiation doses
  - Minimal or no cardiac protection techniques at time of irradiation
  - Cardiac volume exposed to irradiation
  - Young age at irradiation
  - Increasing interval from time of radiation
  - Pre-existing cardiovascular risk factors

**Acute Cardiac Injury**
- (less common)
- Acute pericarditis
- Myocarditis

**Late Cardiac Injury**
- Constrictive pericarditis
- Restrictive cardiomyopathy
- Coronary artery disease
- Valvular disease
- Conduction disturbances

**Medium or Large Vessel Vasculopathy**
- Thoracic aortic calcification (porcelain aorta)
- Carotid/axillary/subclavian artery stenosis

\textsuperscript{1}Cutter DJ et al. Tex Heart Inst J 2011;38:257-258

\textsuperscript{2}Cohn KE et al. Medicine (Baltimore) 1967;46:281-298
Relative risk of RIHD in cancer survivors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hodgkin lymphoma: Relative risk</th>
<th>Breast cancer: Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation induced heart disease</td>
<td>&gt;6.3</td>
<td>2-5.9</td>
</tr>
<tr>
<td>IHD</td>
<td>4.2-6.7</td>
<td>1-2.3</td>
</tr>
<tr>
<td>Valve surgery</td>
<td>8.4-9.2</td>
<td>-</td>
</tr>
<tr>
<td>PPM</td>
<td>1.9</td>
<td>-</td>
</tr>
<tr>
<td>CHF</td>
<td>4.9</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2.2-12.7</td>
<td>0.9-2.0</td>
</tr>
</tbody>
</table>

Ng A. BJH 2011; 154:23-31
<table>
<thead>
<tr>
<th>Table 2</th>
<th>Risk factors of radiation-induced heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anterior or left chest irradiation location</td>
</tr>
<tr>
<td></td>
<td>High cumulative dose of radiation (&gt;30 Gy)</td>
</tr>
<tr>
<td></td>
<td>Younger patients (&lt;50 years)</td>
</tr>
<tr>
<td></td>
<td>High dose of radiation fractions (&gt;2 Gy/day)</td>
</tr>
<tr>
<td></td>
<td>Presence and extent of tumour in or next to the heart</td>
</tr>
<tr>
<td></td>
<td>Lack of shielding</td>
</tr>
<tr>
<td></td>
<td>Concomitant chemotherapy (the anthracyclines considerably increase the risk)</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular risk factors (i.e. diabetes mellitus, smoking, overweight, ≥moderate hypertension, hypercholesterolaemia)</td>
</tr>
<tr>
<td></td>
<td>Pre-existing cardiovascular disease</td>
</tr>
</tbody>
</table>

High-risk patients definition: anterior or left-side chest irradiation with ≥1 risk factors for RIHD.
• 2168 women in Denmark and Sweden treated with RT between 1958-2001
  - 963 women with major coronary events (MI, revascularization, death from IHD)
• Mean dose to whole heart= 4.9 Gy (0.03-27.72)
• Risk increases linearly with mean dose to heart

• Rate of major coronary events increases by 7.4% per Gy

• No apparent threshold below which there is no risk

**Major coronary event defined as MI, revascularization, or death from IHD**

Darby et al. NEJM 2013;368:987-98
Cumulative incidence of cardiac diagnoses and cardiac procedures among 1279 HL patients treated from 1969-1989.

National Comprehensive Cancer Network Clinical Guidelines endorse stress testing at 10 year intervals after treatment is completed in survivors of HL.


{http://www.nccn.org/professional/physician_gls/pdf/hodgkins.pdf}
Baseline pre-radiation comprehensive Echocardiography → CHEST RADIATION EXPOSURE → Yearly targeted clinical history and physical examination → Search for signs and symptoms suggestive of:
- Pericardial effusion/constriction
- Valvular heart disease
- LV dysfunction/heart failure
- Coronary artery disease
- Carotid artery disease
- Conduction system disease → New murmur → Echocardiography → Signs/symptoms of heart failure → Angina → CMR if suspicion of pericardial constriction → Neurological signs/symptoms → Carotid US → Asymptomatic → Functional non-invasive stress test for CAD detection (5 to 10 years after exposure in high risk patients) → Re-assess every 5 years

Table 2  Risk factors of radiation-induced heart disease
- Anterior or left chest irradiation location
- High cumulative dose of radiation (>30 Gy)
- Younger patients (<50 years)
- High dose of radiation fractions (>2 Gy/day)
- Presence and extent of tumour in or next to the heart
- Lack of shielding
- Concomitant chemotherapy (the anthracyclines considerably increase the risk)
- Cardiovascular risk factors (i.e. diabetes mellitus, smoking, overweight, moderate hypertension, hypercholesterolaemia)
- Pre-existing cardiovascular disease

High-risk patients definition: anterior or left-side chest irradiation with ≥1 risk factors for RHDI.
Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

<table>
<thead>
<tr>
<th>Time since Radiotherapy*</th>
<th>No. of Case Patients</th>
<th>No. of Controls</th>
<th>Increase in Rate of Major Coronary Events (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% increase/Gy</td>
</tr>
<tr>
<td>0 to 4 yr</td>
<td>206</td>
<td>328</td>
<td>16.3 (3.0 to 64.3)</td>
</tr>
<tr>
<td>5 to 9 yr</td>
<td>216</td>
<td>296</td>
<td>15.5 (2.5 to 63.3)</td>
</tr>
<tr>
<td>10 to 19 yr</td>
<td>323</td>
<td>388</td>
<td>1.2 (–2.2 to 8.5)</td>
</tr>
<tr>
<td>≥20 yr</td>
<td>218</td>
<td>193</td>
<td>8.2 (0.4 to 26.6)</td>
</tr>
<tr>
<td>0 to ≥20 yr</td>
<td>963</td>
<td>1205</td>
<td>7.4 (2.9 to 14.5)</td>
</tr>
</tbody>
</table>

Harby et al. NEJM 2013;368:987-98

Table 2  Risk factors of radiation-induced heart disease

- Anterior or left chest irradiation location
- High cumulative dose of radiation (>30 Gy)
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- High dose of radiation fractions (>2 Gy/day)
- Presence and extent of tumour in or next to the heart
- Lack of shielding
- Concomitant chemotherapy (the anthracyclines considerably increase the risk)
- Cardiovascular risk factors (i.e. diabetes mellitus, smoking, overweight, ≥ moderate hypertension, hypercholesterolaemia)
- Pre-existing cardiovascular disease

High-risk patients definition: anterior or left-side chest irradiation with ≥ 1 risk factors for RHD.
Echocardiography is the assessment method of choice, and 3D echocardiography may be useful, particularly for the evaluation of mitral valve commissures. Baseline and repeated echocardiography after radiation therapy involving the heart are recommended in patients with cancer for the diagnosis and follow-up of VHD.\textsuperscript{80,85,95,148}
Echocardiographic features of radiation-induced valvular disease

- Left sided valve disease is much more common than right sided valve disease
- Calcification of Ao root, AV annulus and leaflets, and aortic-mitral inter-valvular fibrosa
- Calcification of the MV annulus and leaflets with sparing of the valve tips and commissures
Cardiac surgery & RIHD

- Often multiple cardiac lesions
- Co-existing radiation induced pulmonary disease
- Co-existing vascular disease e.g. porcelain aorta
- Fibrosis of internal mammary artery
- ‘Hostile’ chest
- Tradition surgical risk scores do not consider prior RT and/or chemo: **underestimate** risk

## Adverse outcomes following cardiac surgery in pts with RIHD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Radiation Heart Disease Group (n=173)</th>
<th>Comparison Group (n=305)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±14</td>
<td>63±14</td>
<td>0.9</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>130 (75)</td>
<td>226 (74)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>69 (40)</td>
<td>159 (52)</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>27 (16)</td>
<td>74 (24)</td>
<td>0.07</td>
</tr>
<tr>
<td>Prior stroke, n (%)</td>
<td>18 (10)</td>
<td>24 (8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>63 (36)</td>
<td>113 (37)</td>
<td>0.5</td>
</tr>
<tr>
<td>Proximal obstructive CAD, n (%)</td>
<td>78 (45)</td>
<td>117 (38)</td>
<td>0.09</td>
</tr>
<tr>
<td>Prior open heart surgery, n (%)</td>
<td>34 (20)</td>
<td>87 (29)</td>
<td>0.02</td>
</tr>
<tr>
<td>ICD, n (%)</td>
<td>8 (5)</td>
<td>3 (1)</td>
<td>0.01</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>7.8±3</td>
<td>7.4±3</td>
<td>0.12</td>
</tr>
<tr>
<td>Type of cardiothoracic surgery, n (%)</td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>CABG</td>
<td>24 (14)</td>
<td>47 (15)</td>
<td></td>
</tr>
<tr>
<td>CABG+1 valve</td>
<td>39 (23)</td>
<td>66 (22)</td>
<td></td>
</tr>
<tr>
<td>CABG+≥ 2 valves</td>
<td>37 (21)</td>
<td>64 (21)</td>
<td></td>
</tr>
<tr>
<td>1 Valve only</td>
<td>38 (22)</td>
<td>67 (23)</td>
<td></td>
</tr>
<tr>
<td>≥ 2 Valves</td>
<td>28 (16)</td>
<td>47 (15)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (4)</td>
<td>13 (4)</td>
<td></td>
</tr>
<tr>
<td>Bypass grafts, n</td>
<td>1.2±1.4</td>
<td>1.2±1.6</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Wu et al. Circulation 2013;127:1476-1484
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<tr>
<th>Variable</th>
<th>Radiation Heart Disease Group (n=173)</th>
<th>Comparison Group (n=305)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioperative length of stay, d</td>
<td>17±20</td>
<td>12±20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative permanent atrial fibrillation, n (%)</td>
<td>28 (16)</td>
<td>12 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative permanent pacemaker, n (%)</td>
<td>18 (10)</td>
<td>14 (5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Postoperative stroke, n (%)</td>
<td>1 (0.06)</td>
<td>5 (1.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Mortality within 30 d, n (%)</td>
<td>7 (4)</td>
<td>1 (0.3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

![Cumulative Survival Graph](image1)

![Cumulative Survival Graph](image2)

Number at risk:
- Control group, no prior cardiac surgery: 305, 211, 201, 183, 153, 66, 2
- Control group, prior cardiac surgery: 87, 80, 73, 66, 54, 24, 0
- Radiation group, no prior cardiac surgery: 80, 66, 59, 52, 47, 20, 1
- Radiation group, prior cardiac surgery: 93, 73, 64, 51, 39, 11, 1
Radiation & Cerebrovascular disease

Relative risk of ischemic stroke and TIA

Plummer et al. Stroke 2011;42:2410-2418
Radiation-induced carotid disease

- Increasing rates of hemodynamically significant stenosis with time from RT
- Often more extensive disease
- Involves longer segments of the carotid arteries
- More commonly involves the common carotid

Yu et al. Stroke 2014;45:1402-1407
Pathogenesis of radiation-induced vasculopathy

• Likely a combination of:
  – A. Radiation injury to the vasa vasorum (→ ischemia of the vessel wall)
  – B. Radiation injury to intima-media (endothelium)
→ Accelerated form of atherosclerosis

Source: http://anatomy.kmu.edu.tw
Patients irradiated for head and neck cancer or lymphoma should undergo cerebrovascular ultrasound screening, especially beyond 5 years after irradiation. Duplex imaging may be considered at least every 5 years, or earlier and/or more frequently if the results of the first examination are abnormal. Other locations of post-radiation arterial lesions are usually discovered by clinical examination or when symptomatic.
Management of radiation induced carotid disease

- Radiation vasculopathy not addressed in current guidelines
- Effect of medical rx in limiting disease progression unclear
- Revascularization: Carotid endarterectomy versus (CEA) OR carotid angioplasty and stenting (CAS)?
CEA challenges associated with radiation-induced carotid disease

- Arterial wall fibrosis
- Tissue plane scarring
- Prosthetic infection
- Anastomotic dehiscence
- Surgically inaccessible proximal lesions
- Increased risk of wound complications
- Increased risk of restenosis

Yu et al. Stroke 2014;45:1402-1407
CEA versus CAS for radiation-induced carotid stenosis:

<table>
<thead>
<tr>
<th></th>
<th>Carotid artery angioplasty and stenting (n=361)</th>
<th>Carotid endarterectomy (n=172)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periop cerebrovascular events</td>
<td>3.9% (95% CI, 2.3-6.7%)</td>
<td>3.5% (95% CI, 1.5-8.0%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Late (&gt;30 days) cerebrovascular events</td>
<td>4.9/100 person-years (95% CI, 3.6-6.6)</td>
<td>2.8/100 person-years (95% CI, 2.0-3.9)</td>
<td>0.014</td>
</tr>
<tr>
<td>Cranial nerve injury</td>
<td>0%</td>
<td>9.2% (95% CI, 3.7-21.1%), mostly transient</td>
<td>Significant</td>
</tr>
<tr>
<td>Restenosis &gt; 50%</td>
<td>5.4/100 person years (95% CI, 4.3-6.6)</td>
<td>2.8/100 person-years (95% CI, 1.9-4.0)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Fokkema et al. Stroke 2012;43:793-801
## Carotid angioplasty/stenting in XRT-induced versus other carotid stenosis

<table>
<thead>
<tr>
<th></th>
<th>Radiation-induced carotid stenosis (n=65)</th>
<th>Atherosclerotic carotid stenosis (n=129)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Periprocedural stroke/death</strong></td>
<td>1.5%</td>
<td>1.6%</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Annual risk of stroke</strong></td>
<td>1.2%</td>
<td>1.2%</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Technical success</strong></td>
<td>100%</td>
<td>100%</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Instent restenosis</strong></td>
<td>25.7%</td>
<td>4.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Symptomatic instent restenosis</strong></td>
<td>6.8%</td>
<td>0.8%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Yu et al. Stroke 2014;45:1402-1407
2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Stringent risk factor management is required to halt plaque progression. Antiplatelet therapy may be considered. Significant stenosis (e.g. carotid arteries) may require stenting or surgery.\textsuperscript{201,202}
Changes in radiation field over time for HL

Hodgson DC Hematology 2011:323-329
Techniques to reduce cardiac exposure in RT for breast cancer

- CT assisted planning
- Prone position
- Deep inspiratory breath hold technique
- Intensity modulated radiation therapy
- Accelerated partial breast irradiation

Beck et al. Front Oncol 2014;4:327
Take home points regarding XRT

• Radiation-induced CV injury can manifest in many ways: CAD, valve disease, carotid disease, and PAD.
• Risk factors recognized
• Risk \( \alpha \) mean radiation dose to heart
• Contemporary RT protocols refined to reduce radiation dose to heart...but risk not eliminated
• Annual history and exam
• Periodic ECG, functional stress testing, echo, US carotids
• Extra care with modifiable CV risk factors
• Educate patients regarding risk
• Cardiac surgery for RIHD is associated with increased risk
CANCER SURVIVORS:
* SURVIVORS OF CHILDHOOD CANCERS
* SURVIVORS OF ADULT CANCERS
Survivors of Childhood Cancers

• Current 5-year survival rates approach 80% → growing population of survivors

• Cardiac-specific disease is the most common non-cancer cause of death

• Compared with general population, childhood cancer survivors are at a:
  – 15-fold increased risk of developing CHF
  – 7-fold higher risk of premature cardiac death

Cardiometabolic risk factors among adult survivors of childhood cancers

- Higher than expected frequency of obesity (especially women treated with cranial radiation as girls)
- Excessive adiposity and ↓ lean body mass (check waist circumference, not just BMI)
- Metabolic syndrome-type lipid abnormalities (Low HDL and high triglycerides) even without obesity (lipid panel every 2 years)
- Radiation exposure to hypothalamic-pituitary axis → late onset deficiency of GH → obesity, insulin resistance, and T2DM (screen for altered glucose metabolism every 3 years)
- Predisposition to HTN (monitor BP regularly)

Chronic Health Conditions in Adult Survivors of Childhood Cancer


Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Survivors (N = 10,397)</th>
<th>Siblings (N = 3034)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major joint replacement*</td>
<td>1.61</td>
<td>0.03</td>
<td>54.0 (7.6–386.3)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.24</td>
<td>0.10</td>
<td>15.1 (4.8–47.9)</td>
</tr>
<tr>
<td>Second malignant neoplasm†</td>
<td>2.38</td>
<td>0.33</td>
<td>14.8 (7.2–30.4)</td>
</tr>
<tr>
<td>Cognitive dysfunction, severe</td>
<td>0.65</td>
<td>0.10</td>
<td>10.5 (2.6–43.0)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.11</td>
<td>0.20</td>
<td>10.4 (4.1–25.9)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1.56</td>
<td>0.20</td>
<td>9.3 (4.1–21.2)</td>
</tr>
<tr>
<td>Renal failure or dialysis</td>
<td>0.52</td>
<td>0.07</td>
<td>8.9 (2.2–36.6)</td>
</tr>
</tbody>
</table>
Dose-response relationship for cardiomyopathy

Recommendations for Cardiomyopathy Surveillance for Survivors of Childhood Cancer: A Report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Saro H. Armenian¹, Melissa M. Hudson², Renee L. Mulder³, Ming Hui Chen⁴, Louis S. Constine⁵, Mary Dwyer⁶, Paul C. Nathan⁷, Wim J.E. Tissing⁸, Sadhna Shankar⁹, Elske Sieswerda³, Rod Skinner¹⁰, Julia Steinberger¹¹, Elvira C. van Dalen³, Helena van der Pal¹², W. Hamish Wallace¹³, Gill Levitt¹⁴, and Leontien C.M. Kremer³

Cardiomyopathy risk group definitions.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Anthracycline dose (mg/m²)</th>
<th>Chest radiation dose (Gy)</th>
<th>Anthracycline (mg/m²) + Chest radiation (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>≥ 250</td>
<td>≥ 35</td>
<td>≥ 100 (Anthracycline) + ≥ 15 (Radiation)</td>
</tr>
<tr>
<td>Moderate</td>
<td>100 to &lt; 250</td>
<td>≥ 15 to &lt; 35</td>
<td>--</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 100</td>
<td>--</td>
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</tr>
<tr>
<td>Low</td>
<td>&lt; 100</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

- CMP surveillance **is recommended** for high risk survivors to begin no later than 2 years after rx, repeated at 5 years, and continued every 5 years thereafter.
- CMP surveillance **is reasonable** for moderate/low risk survivors over same time frame
Efficacy and Cost-effectiveness of the Children’s Oncology Group Long-Term Follow-Up Screening Guidelines for Childhood Cancer Survivors at Risk of Treatment-related Heart Failure

F. Lennie Wong, PhD, Smita Bhatia, MD, MPH, Wendy Landier, PhD, RN, Liton Francisco, BS, Wendy Leisenring, ScD, Melissa M. Hudson, MD, Gregory T. Armstrong, MD, Ann Mertens, PhD, Marilyn Stovall, PhD, Leslie L. Robison, PhD, Gary H. Lyman, MD, MPH, Steven E. Lipshultz, MD, and Saro H. Armenian, DO, MPH

Routine echocardiography screening for left-ventricular dysfunction in childhood cancer survivors: a model-based estimation of the clinical and economic impacts

Jennifer M. Yeh, PhD, Anju Nohria, MD, and Lisa Diller, MD
• Prospective LVEF assessment at baseline, every 3 months during Rx and for the following year, and then every 6 months for the following 4 years in 2625 pts receiving anthracyclines
• Overall incidence of cardiotoxicity (LVEF decrease > 10 percentage points from baseline and < 50%) = 9%
• Median interval from end of chemo to cardiotox = 3.5 months
• 98% of cases occurred in the first year
Criteria for INCREASED RISK in survivors of adult cancers:

- Treatment that includes any of the following:
  - High-dose anthracycline (eg, doxorubicin \( \geq 250 \, \text{mg/m}^2 \), epirubicin \( \geq 600 \, \text{mg/m}^2 \))
  - High-dose radiotherapy (RT; \( \geq 30 \, \text{Gy} \)) where the heart is in the treatment field
  - Lower-dose anthracycline (eg, doxorubicin < 250 mg/m², epirubicin < 600 mg/m²) in combination with lower-dose RT (< 30 Gy) where the heart is in the treatment field
- Treatment with lower-dose anthracycline (eg, doxorubicin < 250 mg/m², epirubicin < 600 mg/m²) or trastuzumab alone, and presence of any of the following risk factors:
  - Multiple cardiovascular risk factors (\( \geq \text{two risk factors} \)), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after completion of therapy
  - Older age (\( \geq 60 \, \text{years} \)) at cancer treatment
  - Compromised cardiac function (eg, borderline low left ventricular ejection fraction [50% to 55%], history of myocardial infarction, \( \geq \text{moderate valvular heart disease} \)) at any time before or during treatment
- Treatment with lower-dose anthracycline (eg, doxorubicin < 250 mg/m², epirubicin < 600 mg/m²) followed by trastuzumab (sequential therapy)
What to do AFTER completion of cancer treatment?:

Recommendation 5.2. An echocardiogram may be performed between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of cardiac dysfunction. (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 5.3. Patients identified to have asymptomatic cardiac dysfunction during routine surveillance should be referred to a cardiologist or a health care provider with cardio-oncology expertise for further assessment and management. (Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

Recommendation 5.4. No recommendations can be made regarding the frequency and duration of surveillance in patients at increased risk (Recommendation 1.1) who are asymptomatic and have no evidence of cardiac dysfunction on their 6- to 12-month post-treatment echocardiogram. (Informal consensus; relative balance of benefits and harms; Evidence quality: insufficient)

Recommendation 5.5. Clinicians should regularly evaluate and manage cardiovascular risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity in patients previously treated with cardiotoxic cancer therapies. A heart-healthy lifestyle, including the role of diet and exercise, should be discussed as part of long-term follow-up care. (Evidence based and consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
Impaired exercise capacity

- Exercise capacity is below age and sex norms in as many as 31% of long-term pediatric cancer survivors.
• Adult survivors of ALL are at increased CV risk
• Peak VO2 was measured in 115 ALL survivors (median age 23.5 years; range 18-37)
• Compared to age, gender, race/ethnicity controls from the 2003-2004 NHANES cohort
For any given percent body fat, ALL survivors had an 8.9 ml/kg/min lower VO2 max than non-cancer controls.
Impaired exercise capacity

- Exercise capacity is below age and sex norms in as many as 31% of long term pediatric cancer survivors.

- Among survivors of adult cancers, impaired exercise capacity is prevalent:
  - “I can’t go as far as I used to”
  - “I tire easily”
  - “I can’t keep up with my husband anymore”
Evaluated cardiopulmonary function across the breast cancer continuum:

- Before adjuvant therapy for nonmetastatic disease (n=20)
- During adjuvant therapy for nonmetastatic disease (n=46)
- After adjuvant therapy for nonmetastatic disease (n=130)
- During therapy for metastatic disease (n=52)
Mean Peak VO2

Mean LVEF of cohorts >= 59%

Hypothesis: similar patterns of cardiovascular perturbations are present in CRC and CHF

Methods: Prospectively studied 3 groups:
- CRC group (n= 50; 26 received chemo and 24 were chemo naïve)
- CHF group (n= 51)
- Control group (n=51)
Exercise capacity in colorectal cancer pts is severely impaired compared with age-matched controls (mean peak VO2 23% below controls)

Peak VO2 was only ~17% higher than that of HF pts

Independent of chemotherapy

Cramer et al. JACC 2014; 64:1310-9
Exercise capacity & prognosis

Table 2. Age-Adjusted and Multivariable-Adjusted Relative Risks According to Physical Activity Category After Breast Cancer Diagnosis

<table>
<thead>
<tr>
<th>Physical Activity After Diagnosis, MET-h/wk</th>
<th>Total (N = 2987)</th>
<th>&lt;3 (n = 959)</th>
<th>3-8.9 (n = 862)</th>
<th>9-14.9 (n = 335)</th>
<th>15-23.9 (n = 428)</th>
<th>≥24 (n = 403)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>463</td>
<td>188</td>
<td>126</td>
<td>38</td>
<td>51</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.00</td>
<td>0.69 (0.55-0.87)</td>
<td>0.53 (0.37-0.75)</td>
<td>0.56 (0.41-0.77)</td>
<td>0.67 (0.50-0.90)</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted RR (95% CI)*</td>
<td>1.00</td>
<td>0.71 (0.56-0.89)</td>
<td>0.59 (0.41-0.84)</td>
<td>0.56 (0.41-0.77)</td>
<td>0.65 (0.48-0.88)</td>
<td>.003</td>
<td></td>
</tr>
</tbody>
</table>

Holmes et al. JAMA 2005;293:2479-2486
Impaired Exercise Capacity in Cancer Patients

• Evidence of impaired exercise capacity

• Exercise capacity in cancer survivors influences:
  – All-cause mortality
  – Cancer mortality
  – ?? Cancer recurrence

• ∴ impaired exercise capacity in cancer patients that is prognostically significant.

• But why is exercise capacity impaired in cancer survivors?
Impaired Exercise Capacity & Cardiac Autonomic Dysfunction

• Cancer- and cancer treatment-mediated injury to myocardium, pericardium, valves, coronaries, and large vessels well described.....

• Logical that the cardiac autonomic nervous system also vulnerable to injury?
Case

- 34 year old female
- Stage IIa Hodgkin lymphoma 2003 (age 21)
  - 4 cycles ABVD chemotherapy (cumulative anthracycline dose=200 mg/m²)
  - 36.6 Gy mantle radiation
- C/o exercise induced fatigue. No SOBOE
- Clinical exam:
  - HR at rest = 95 bpm, reg
  - Weight= 52kg
  - Unremarkable
- Labs:
  - Normal CBC, renal, liver profiles
  - TSH= 4.66  TC= 156  LDL= 66  HDL= 63
- TTE: LVEF=65%, normal diastology, normal valves
Resting ECG: HR = 107 bpm
50 seconds into exercise: HR = 157 bpm
10 mins 2 seconds exercise: HR= 203 bpm
1 minute into recovery: HR= 176 bpm
3 minutes into recovery: HR= 141 bpm
14 minutes into recovery: HR= 131 bpm
What does this mean?

• 34 year old female HL survivor
  – 13 years post-anthracycline chemotherapy (200 mg/m²) and mantle radiation (36.6 Gy)

• Exertional fatigue

• No evidence of LV systolic or diastolic dysfunction

• Elevated resting HR, rapid HR acceleration after onset of exercise, and slow deceleration post-exercise
Abnormal Exercise Response in Long-Term Survivors of Hodgkin Lymphoma Treated With Thoracic Irradiation

Evidence of Cardiac Autonomic Dysfunction and Impact on Outcomes

John D. Groarke, MBBS, MPH,* † Varsha K. Tanguturi, MD, * Jon Hainer, BS, † Josh Klein, BA, † Javid J. Mosleh, MD, † Andrea Ng, MD, § Daniel E. Forman, MD, * † Marcelo F. Di Carli, MD, * † Anju Nohria, MD †

<table>
<thead>
<tr>
<th>Variable</th>
<th>Radiation Patients (n = 263)</th>
<th>Control Patients (n = 526)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>49.9 ± 11.0</td>
<td>49.7 ± 10.8</td>
<td>0.77</td>
</tr>
<tr>
<td>Male</td>
<td>121 (46.0)</td>
<td>228 (43.4)</td>
<td>0.49</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.3 ± 5.6</td>
<td>27.7 ± 6.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>78 (30.0)</td>
<td>171 (32.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (5.3)</td>
<td>34 (6.5)</td>
<td>0.64</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>130 (49.4)</td>
<td>203 (38.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>90 (46.2)</td>
<td>174 (45.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Smoking history</td>
<td>13 (4.9)</td>
<td>43 (8.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>26 (9.9)</td>
<td>60 (11.4)</td>
<td>0.55</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>41 (15.6)</td>
<td>52 (9.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Morise score</td>
<td>9 (3 to 12)</td>
<td>9 (4 to 12)</td>
<td>0.92</td>
</tr>
<tr>
<td>Cardiovascular medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>58 (22.1)</td>
<td>120 (22.8)</td>
<td>0.86</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>18 (6.8)</td>
<td>41 (7.8)</td>
<td>0.70</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>33 (12.6)</td>
<td>79 (15.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Diuretic</td>
<td>23 (8.8)</td>
<td>54 (10.3)</td>
<td>0.53</td>
</tr>
<tr>
<td>Statin</td>
<td>96 (36.5)</td>
<td>146 (27.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age at time of RT, yrs</td>
<td>30.0 ± 12.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Interval from RT to ETT, yrs</td>
<td>19 (12-26)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total radiation dose, Gy</td>
<td>38 (36-40)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Adjuvant anthracycline chemotherapy</td>
<td>121 (46.0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LV ejection fraction, %*</td>
<td>59.0 ± 5.3</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
*** = p<0.0001 by univariate comparisons
Likelihood of AD in HL survivors versus controls

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Primary endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated resting heart rate</td>
<td>3.68 (2.65–5.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abnormal heart rate recovery at 1 min</td>
<td>4.57 (3.09–6.76)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, Morise risk score, diabetes, indication for ETT, AVN-blocking medications, congestive heart failure/IHD, and anthracycline exposure. †Adjusted for age, sex, Morise risk score, diabetes, indication for ETT, AVN-blocking medications, congestive heart failure/IHD, resting HR, exercise time, result of ETT, and anthracycline exposure. ‡Adjusted for age, sex, Morise risk score, diabetes, indication for ETT, antihypertensive medications, congestive heart failure/IHD, resting HR, exercise time, result of ETT, and anthracycline exposure.

Functional Implications:
Reductions in exercise capacity

- Among HL survivors treated with RT:
  - Elevated resting HR associated with an adjusted* mean reduction of 1.1±0.4 in METs achieved during ETT (p=0.002)
  - Abnormal HRR associated with an adjusted* mean reduction of 1.0±0.4 in METs achieved during ETT (p=0.007)

*Adjusted for age, sex, CV risk factors, medications, indication for ETT, result of ETT

Groarke JD, et al. JACC 2015; 65:573-83
Prevalence of cardiac AD according to time from treatment

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer cohort (n=448)</th>
<th>Control cohort (n=448)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62.6±10.0</td>
<td>62.5±10.0</td>
<td>0.92</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.0±5.2</td>
<td>28.8±6.3</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR HISTORY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morise risk score</td>
<td>13.5 (11.0, 16.0)</td>
<td>13.5 (11.0, 16.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>229 (51.1%)</td>
<td>254 (56.7%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>221 (49.3%)</td>
<td>265 (59.2%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>49 (10.9%)</td>
<td>86 (19.2%)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>39 (8.7%)</td>
<td>61 (13.6%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>23 (5.1%)</td>
<td>39 (8.7%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>28 (6.3%)</td>
<td>19 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>64.4±9.8 (n=278)</td>
<td>66.9±9.3 (n=208)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Groarke JD, et al. ESC Congress 2016
Elevated resting HR and abnormal HRR

Prevalence in Cohort

Breast Cancer Cohort
Control Cohort

p = 0.013
p = 0.048
P = 0.025
<table>
<thead>
<tr>
<th></th>
<th>Adjusted* mean reduction (SE) in METs achieved</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated resting HR</td>
<td>-0.9 (0.3)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Abnormal HRR</td>
<td>-1.3 (0.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Elevated resting HR + Abnormal HRR</td>
<td>-1.9 (0.4)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, hypertension, ischemic heart disease, hyperlipidemia, smoking history, diabetes mellitus, statin therapy, AV blocking drugs, result of ETT.

Groarke JD, et al. ESC Congress 2016
Exercise Training

Aerobic Exercise Training

- Oxidative Stress
  - ↑Antioxidants
  - ↓ROS
- Nitric Oxide
  - ↑Nitric Oxide
- RAAS
  - ↓Angiotensin II
  - ↓Renin

↓Sympathetic Tone  ↑Vagal Tone

Autonomic Function
- ↓Resting HR
- ↑HRV
- ↑Baroreflex Sensitivity

Scott et al. Int J Cardiol 2014;171:e50-e51
Summary of studies investigating the cardiovascular effects of exercise interventions after completion of breast cancer treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient population</th>
<th>Exercise intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courneya et al. 2003 [62]</td>
<td>53 post-menopausal breast cancer survivors after completion of surgery, radiotherapy, and/or chemotherapy</td>
<td>Supervised aerobic exercise, 15 – 35 min/d at 70 % – 75 % of VO$_{2peak}$, 3 d/wk × 15 wks ($n = 25$); or control ($n = 28$).</td>
<td>↑ VO$_{2peak}$ and ↑ self-reported QOL with aerobic exercise compared to control.</td>
</tr>
<tr>
<td>Daly et al. 2006 [73]</td>
<td>108 women treated for breast cancer 12 to 36 months previously</td>
<td>Supervised aerobic exercise, 50 min/d at 65 % – 85 % maximum heart rate and RPE 12–13, 3 d/wk × 8 wks ($n = 34$); exercise-placebo, 50 min/d of light-intensity body conditioning/stretching, 3 d/wk × 8 wks ($n = 36$); or usual care ($n = 38$).</td>
<td>↑ fitness measured by submaximal walking test with aerobic exercise and exercise-placebo compared to usual care.</td>
</tr>
<tr>
<td>Hutnick et al. 2005 [74]</td>
<td>49 survivors of stage I–III breast cancer</td>
<td>Supervised aerobic exercise, 10 – 20 min/d at 60 % – 75 % of VO$_{2peak}$, plus resistance training, total session 40–90 min/d, 3 d/wk × 6 months ($n = 28$); or control ($n = 21$).</td>
<td>↑ VO$_{2peak}$ and ↑ upper body strength</td>
</tr>
<tr>
<td>Pinto et al. 2005 [75]</td>
<td>86 women after completing treatment for stage 0–II breast cancer</td>
<td>Home-based aerobic exercise, 10 – 30 min/d at 55 % – 65 % of maximum heart rate, 5 d/wk × 12 wks ($n = 43$); or control ($n = 43$)</td>
<td>↑ fitness (↓ time for 1-mile walk test); no change in BMI or % body fat with aerobic exercise compared to control.</td>
</tr>
<tr>
<td>Schneider et al. 2007 [63]</td>
<td>113 women with breast cancer; 96 completed radiation and/or chemotherapy, and 17 undergoing concurrent cancer treatment with exercise</td>
<td>Supervised aerobic exercise, 60 min/d at 40 %–75 % of heart rate reserve, 2–3 d/wk × 6 months</td>
<td>↑ VO$_{2peak}$, ↓ SBP, ↓ resting heart rate, ↓ fatigue with aerobic exercise after completion of cancer treatment.</td>
</tr>
</tbody>
</table>
Take home points on survivorship I

• Survivors of childhood cancers = cohort with adverse CV outcomes
• Unfavorable cardiometabolic profile: sarcopenic obesity, metabolic syndrome, insulin resistance --> regular surveillance of BMI, waist circumference, lipid panel, HbA1c
• Survivors of childhood cancers can be risk stratified based on cumulative anthracycline and radiation exposure
• CMP surveillance recommended for high risk survivors within 2 years of rx, and repeated q5 yrs (reasonable for moderate/low risk survivors)
Take home points on survivorship II

- Criteria for increased risk among survivors of adult cancers
- Echo 6-12 months after rx in asymptomatic ‘increased risk’ pts
- Evidence of impaired exercise capacity in cancer patients that is prognostically significant - multiple factors contribute to exercise limitation.
- Encourage cancer survivors of the need for exercise
- Aggressive optimization of modifiable CV risk factors
- Educate pts of risk, signs and symptoms of IHD, CVD, and PAD
- Providers should retain a high index of suspicion for CV disease and a low threshold for testing/intervention
Thank You

John Groarke
jgroarke@partners.org