Radiation Therapy Essentials: How to Care for Patients Treated Then and Now

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Clinical Case

- 57 yo female w/ HL in 1979
- Staging laparotomy, splenectomy
- Mantle and para-aortic RT, 36 Gy
- 6 mth h/o DOE, orthopnea, abd bloating, pedal edema
- Denies chest pain, palpitations, lightheadedness
- No other CRF except obesity

- HR 95 bpm BP 124/82 Wt 200 lbs
- JVP 16 cm water, 1+ carotids w/ bilateral bruits
- Decreased breath sounds at R base
- RRR. NI S1. Audible single S2. Mid-peaking systolic crescendo-decrescendo murmur @ base w/ radiation to the carotids. Soft, early diastolic murmur @ base. No mid-systolic click. Soft diastolic rumble at apex.
- 2+ bilateral LE edema
Trends in RT Among Cancer Survivors

SEER: 2000-2030
• ~30% treated w/ RT

Bryant et al. 2017 Cancer Epidemiol Biomarkers Prev.
## Radiation Induced Heart Disease

<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 cardiovascular disease</td>
<td>&gt;6.3</td>
<td>2-5.9</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>4.2-6.7</td>
<td>1-2.3</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>8.4-9.2</td>
<td>-</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>1.9</td>
<td>-</td>
</tr>
<tr>
<td>Congestive heart failure</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>

Pathogenesis of RT-Induced Heart Disease

### Table 2  Risk factors of radiation-induced heart disease

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

High-risk patients definition: anterior or left-side chest irradiation with ≥1 risk factors for RIHD.
Dose Dependent Risk of RIHD

- N=2168 women treated w/ RT for breast CA from 1958-2001
- Mean dose to the heart = 4.9 Gy
- N=963 women w/ MI, revascularization, death from IHD
- 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

Darby et al. NEJM 2013;368:987-98
Younger Age is a Risk Factor for RT-Induced CVD

1474 HL survivors, Rx’ed 1965-95

2524 HL survivors, Rx’ed 1965-95

Time Dependent Risk of RT

- Cumulative incidence of cardiac diagnoses and procedures among 1279 HL survivors, treated between 1969-89.

Cumulative incidence @ 40 yrs:
- 54.6% for any CVD
- 22.9% for MI
- 25.9% for valvular dz
- 8.1% for primary CHF
- 24.8% for any CHF


National Comprehensive Cancer Network Clinical Guidelines endorse stress testing at 10 year interval after treatment in survivors of HL

(http://www.nccn.org/professional/physician_gls/pdf/hodgkins.pdf)

Increased Incidence of Autonomic Dysfunction in HL Survivors

- ↑ Incidence of:
  - Elevated resting HR
  - Abnormal HRR
  - Abnormal BP response to exercise

- RF for autonomic dysfxn:
  - ↑ RT dose
  - ↑ Time from RT
  - Mantle RT

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>ELEVATED RESTING HEART RATE*</th>
<th>ABNORMAL HEART RATE RECOVERY†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise Duration</td>
<td>- 1.1 ± 0.3, p = 0.001</td>
<td>- 1.0 ± 0.4, p = 0.006</td>
</tr>
<tr>
<td>Mortality, HR (95% CI)</td>
<td>0.99 (0.40-2.45)</td>
<td>5.50 (1.97-15.36)</td>
</tr>
</tbody>
</table>

Relative to radiation patients without elevated resting heart rate*/with normal heart rate recovery†

RT-Induced Cerebrovascular Disease

- 415 Hodgkin’s survivors

<table>
<thead>
<tr>
<th>Subset of Patients at Risk</th>
<th>Cardiac Sequelae (n = 404)*</th>
<th>Arterial Sequelae (n = 404)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of Patients (n = 415)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve (n = 25)</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>CAD (n = 42)</td>
<td>30</td>
<td>227</td>
</tr>
<tr>
<td>No Sequelae (n = 348)</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>Carotid or Subclavian (n = 30)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>No Sequelae (n = 374)</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

Sex:
- Men: 253
- Women: 162

Median age at Hodgkin lymphoma diagnosis, range, y:
- Men: 25 (16-75)
- Women: 22 (5-48)

Median time to event, range, y:
- Men: 9 (1-32)
- Women: 22 (6-31)

- 431 CCS (265 w/ cranial RT)

Hull JAMA 2003;290:2831

- 290 pts with head & neck ca
- carotid u/s 2 yrs after XRT

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>Total (n = 290)</th>
<th>Tis (n = 192)</th>
<th>No (n = 98)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid artery stenosis (CAS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAS ≥ 5.0%</td>
<td>38 (13.1)</td>
<td>38 (19.8)</td>
<td>0 (0.0)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>CAS &gt; 70%</td>
<td>17 (5.9)</td>
<td>17 (8.9)</td>
<td>0 (0.0)</td>
<td>.002*</td>
</tr>
<tr>
<td>CAS = 100%</td>
<td>4 (1.4)</td>
<td>4 (2.1)</td>
<td>0 (0.0)</td>
<td>.150</td>
</tr>
</tbody>
</table>


Screening Algorithm for RT Survivors

PCI Outcomes in RT Survivors

N=116 RT vs. 408 controls


N=157 XRT pts vs. 157 controls

Fender et al. Am Heart J 2017;187:98-103
Cardiac Surgery Outcomes in RT Survivors

N=173 RT pts vs. 305 controls


N=135 RT pts vs. 137 controls

AVR

Donnellan E et a. JAHA 2017;6(5):e005396
Pericardiectomy Outcomes in RT Survivors

Pacemaker Management in Patients Undergoing RT

- Relocate device if:
  - Interfering w/ optimal delivery of RT
  - PPM dependent w/ ipsilateral tumor (eg. breast or lung)

Summary

• Mediastinal RT has significant long-term adverse CV effects
• Routine CV screening recommended for early detection, prevention, and intervention
• Worse outcomes relative to non-irradiated controls, esp. with surgery
• Research needed to identify preventive strategies
A 40 y.o. woman with a history of Stage IIB classical Hodgkin lymphoma at age 19 presents for routine evaluation. She was treated with 6 cycles of ABVD (cumulative anthracycline dose = 300 mg/m²) and 30 Gy of mediastinal radiation (including a node along the right heart border, bilateral subclavian veins and lower neck). She reports that ever since her treatment, she becomes dyspneic when running or walking up an incline, but has no limitations on flat ground. Her exam is unremarkable. Her EKG shows sinus tachycardia at 90 bpm and borderline LVH.
Question

Which of the following are the next most appropriate steps in her management?

• A. No further testing and provide reassurance
• B. 24 hour ambulatory blood pressure monitor
• C. Baseline and stress-echocardiogram
• D. Coronary CT angiogram