Mechanisms of cardiovascular disease in irradiated cancer patients and the influence of ErbB2 blocking agents

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Radiotherapy fields for Hodgkin’s lymphoma
(30-40 Gy: RR fatal CVD 2-7)
Radiotherapy increases risk of congestive heart failure in > 1,400 HL patients


<table>
<thead>
<tr>
<th>Condition</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>7.4</td>
<td>(1.8-30.0)</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>7.0</td>
<td>(2.6-18.9)</td>
</tr>
<tr>
<td>Angina</td>
<td>4.9</td>
<td>(2.0-12.0)</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>2.4</td>
<td>(1.1-5.2)</td>
</tr>
</tbody>
</table>
Increased risk of cardiovascular disease in survivors of childhood cancer

- N >14,000
- Increased risks of MI, CHF, pericardial and valve disease
- HR 2.0-6.0 for >15 Gy

Mulrooney et al. BMJ 2009

<table>
<thead>
<tr>
<th>Mean heart dose (Gy)</th>
<th>N</th>
<th>RR CVD mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1252</td>
<td>1</td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>1243</td>
<td>3.0 (0.3-28)</td>
</tr>
<tr>
<td>1-5</td>
<td>508</td>
<td>2.5 (0.2-41.5)</td>
</tr>
<tr>
<td>5-15</td>
<td>421</td>
<td>12.5 (1.4-116.1)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>541</td>
<td>25.1 (3.0-209.5)</td>
</tr>
</tbody>
</table>

- N >4,000
- Risk of cardiac mortality linearly related to cardiac dose
- ERR at 1 Gy 60%

Tukenova et al. JCO 2010
Reconstructed dose estimates for RT techniques for breast cancer 1950-1990

RT planning for left tangential pair fields

- RCA: Mean 2 Gy
- LADCA: Mean 22 Gy
- Circumflex CA: Mean 3 Gy
- Mean 5 Gy
Risks for incidence of heart disease in women treated with RT for breast cancer

- 72,134 breast cancer patients in Denmark and Sweden (1976-2006)
- 48% received radiotherapy
- Mean heart dose 6.3 Gy for left and 2.7 Gy for right-sided tumors
- Mean dose LADCA ≥15 Gy for left and 1-2 Gy for right-sided tumors

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Incidence (L/R)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarct</td>
<td>1.22</td>
<td>0.007</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1.61</td>
<td>0.03</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>1.70</td>
<td>0.009</td>
</tr>
<tr>
<td>All heart disease</td>
<td>1.08</td>
<td>0.01</td>
</tr>
</tbody>
</table>

McGale et al. Radiotherapy & Oncology 2011
Risk of IHD versus mean heart dose:

Case control study 2168 Swedish/Danish breast cancer patients irradiated 1958-2001

7.4% per Gy (CI 2.9-14.5)

Darby et al. NEJM 2013
## Cardiac dose reduction using modern CT-based RT

Risk major coronary event estimated for left sided breast cancer patients

<table>
<thead>
<tr>
<th>RT position</th>
<th>Mean cardiac dose (Gy)</th>
<th>Excess Risk (low baseline risk)</th>
<th>Excess Risk (high baseline risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>supine</td>
<td>2.17</td>
<td>0.22</td>
<td>3.52</td>
</tr>
<tr>
<td>prone</td>
<td>1.03</td>
<td>0.09</td>
<td>1.31</td>
</tr>
</tbody>
</table>

*Brenner et al. JAMA 2014

IMRT techniques associated with large volume cumulative doses of 2-3 Gy

*Borst et al. IJROBP 2010*
Research questions

• What are the pathologies and mechanisms underlying radiation cardiovascular disease?

• What is the contribution of coronary artery disease (atherosclerosis) versus microvascular damage?

• Is mean dose to the heart sufficient to calculate risk or is dose distribution important?

• Are there different mechanisms after low (<2 Gy) and high (>5 Gy) doses?
Cardiac pathologies

• **Myocardial infarct**: Coronary artery atherosclerosis
• **Congestive heart failure**: Interstitial myocardial fibrosis, diffuse ischemia secondary to decreased capillary density and perfusion
• **Valvular disease**: Rheumatic inflammation or secondary to damaged papillary muscles
• **Pericarditis**: Inflammatory response of epicardium
• **Arrhythmia and conduction defects**: Damage to sinus or AV node (local ischemia and fibrosis)
Radiation-induced atherosclerosis
Interaction between hypercholesterolemia and radiation (aortic root lesions)

Tribble et al., ATVB 1999

8 Gy / HFD

8 Gy / chow

Aortic root

Aortic valves

aortic lesion area ($\mu$m$^2 \times 1000$)

time between Irradiation and initiation of the high-fat diet (days)

*
Increased number of lesions in irradiated carotid arteries ApoE-/- mice

- Increased total plaque area in arteries of irradiated ApoE-/- mice
- No “out of field” effects in ApoE-/- mice
- No lesions in irradiated wild type mice

Stewart et al., AJP 2006; Hoving et al., IJROBP 2008
Analysis of plaques in ApoE\(^{-/-}\) mice:

Stewart et al., AJP 2006

Initial lesion
- Macrophage rich
- No fibrous cap

Advanced lesion
- Necrotic lipid core
- Fibrous cap
Thrombotic phenotype of lesions of irradiated carotid arteries ApoE-/- mice

Stewart et al., AJP 2006; Hoving et al., IJROBP 2008
Decreased collagen content in advanced lesions in irradiated carotid arteries

Hoving et al., IJROBP 2008
Irradiation of existing lesions increases inflammation by favoring type 1 MΦ

Gabriels et al R&O 2014
High dose irradiation increases leukocyte adhesion via chemokine signaling from EC to leukocytes

- Doses 5-15 Gy increased leukocyte adhesion to human aortic EC under physiological shear stress (flow chamber)
- No increase in ICAM1 or VCAM1 but blocking leucocyte integrin receptors with PTX inhibits radiation induced adhesion

*Khaled et al. Radiat Res 2012*
Low dose irradiation decreases leukocyte adhesion and inhibits atherosclerosis

- Doses <1 Gy decreased leukocyte adhesion \textit{in vitro}, via decreased liberation of E-selectin (no increased expression ICAM1)

- TBI <0.5 Gy inhibited atherosclerosis in aortic root

Recent results from EU Procardio project show \textit{increased} plaque area after 0.3 Gy

(Anna Saran)

\textit{Hildebrandt et al. IJRB 2002}\hspace{1cm}\textit{Mitchel et al. Rad Res 2011}
Summary of data on radiation-induced atherosclerosis

- Radiation independent risk factor for atherosclerosis (interaction cholesterol and radiation)
- TBI, but not local irradiation, increases serum cholesterol
- Hypercholesterolemia alone not sufficient to drive atherosclerosis; MΦ/monocyte invasion of vessel wall also required
- Doses 2-8 Gy (aortic root) initiate atherosclerosis and predisposes to thrombotic, inflammatory plaques
- Irradiation of existing plaque increases inflammatory content of lesion and favors type 1 MΦ
- Doses ≤ 0.5 Gy inhibit inflammatory response (and atherosclerosis?)
- P/E-selectin and ICAM1/VCAM1 involved in initiation of radiation-induced atherosclerosis
Radiation-induced cardiac microvascular damage and inflammation
Irradiation set up and schedules
Wild type male C57Bl6 mice; ApoE-/- mice (elevated cholesterol levels)

Allowing for margins and individual anatomical variation:
10.6 x 15.0 mm field
(33% lung in field)

Seemann et al. R&O 2012
Gabriels et al R&O 2012
Restrictive pericarditis: WT hearts 20-40 weeks

Epicardial thickness (µm)

Seemann et al. R&O 2012
Epicardial inflammation: WT hearts 20-40 weeks after irradiation

Seemann et al. R&O 2012