Mechanisms and dose response relationship for radiation-induced cardiovascular damage

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• Epidemiological evidence and dose response relationships from irradiated cancer patients

• Experimental models and mechanisms of development of damage
Radiation as an independent risk factor for cardiovascular disease in long-term survivors of cancer

- Many risk factors for CVD, large studies (preferably randomized trials) and careful analysis needed to confirm radiation as a causal factor

- **Early breast cancer:**
  RR fatal CVD RT vs no RT; EBCT = 1.3

- **Hodgkin’s lymphoma:**
  RR fatal CVD 2-7; higher risks for children
  RR stroke 4.3

- **Childhood cancers:**
  RR 2-6 for cardiac mortality
Risks for cardiac death in women randomized to receive RT vs no RT for breast cancer

<table>
<thead>
<tr>
<th>Category</th>
<th>Mean cardiac dose (Gy)*</th>
<th>Events/Women Allocated Radio.</th>
<th>Events/Women Allocated Control</th>
<th>Radio. events Logrank O-E</th>
<th>Variance of O-E</th>
<th>Ratio of annual event rates Radio.: Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3</td>
<td>145/5040 (2.9%)</td>
<td>117/4942 (2.4%)</td>
<td>4.8</td>
<td>60.2</td>
<td>1.08 (SE 0.13)</td>
</tr>
<tr>
<td>5 - 15</td>
<td>9</td>
<td>237/4374 (5.4%)</td>
<td>170/4476 (3.8%)</td>
<td>26.0</td>
<td>94.5</td>
<td>1.32 (SE 0.12)</td>
</tr>
<tr>
<td>15+</td>
<td>17</td>
<td>125/1140 (11.0%)</td>
<td>72/1125 (6.4%)</td>
<td>22.7</td>
<td>46.2</td>
<td>1.63 (SE 0.19)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10</td>
<td>162/5019 (3.2%)</td>
<td>157/5045 (3.1%)</td>
<td>12.7</td>
<td>67.6</td>
<td>1.21 (SE 0.13)</td>
</tr>
</tbody>
</table>

(c) Dosimetric estimate of cardiac dose (Gy)*

Test for trend: $\chi^2 = 4.4; 2p = 0.04$
Risk ratio per 10 Gy cardiac dose* 1.31 SE 0.07; 2p < 0.0001

Total

<table>
<thead>
<tr>
<th></th>
<th>669/15573 (4.3%)</th>
<th>516/15588 (3.3%)</th>
<th>66.3 268.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>99% or</td>
<td>95% CI</td>
<td></td>
<td>Radio. better</td>
</tr>
<tr>
<td>Treatment effect 2p = 0.00005, adverse</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increase in relative risk of death per 10 Gy mean heart dose = 31%

EBCTCG 2006: PROVISIONAL RESULTS
Risks for incidence of heart disease in women treated with RT in Denmark and Sweden

- 72,134 women diagnosed with breast cancer (1976-2006)
- 34,825 (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 ratio (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>Angina</td>
<td>1.25</td>
<td>0.01</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_
Increased risk of cardiovascular disease in survivors of childhood cancers

• >14,000 5-year survivors, treated 1970-1986 (mean FU 20 years)
• Increased incidence (cf siblings) of myocardial infarct, congestive heart disease, pericardial disease and valvular abnormalities
• HR 2.0-6.0 for cardiac doses >15 Gy (~ equivalent to 7 Gy S/D )

**Congestive heart failure: HR 5.9**

Mulrooney et al., BMJ 2009
Increased risk of cardiovascular disease in survivors of childhood cancers

- 4,122 5-year survivors diagnosed before 1986 in France and UK mean FU 27 years
- ERR cardiac mortality linear function of mean heart dose
  ERR at 1 Gy, 60%

<table>
<thead>
<tr>
<th>Mean heart dose (Gy)</th>
<th>No of patients</th>
<th>RR CVD mortality</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>

Tukenova et al., JCO 2010
Research questions

• Is the etiology of radiation-induced atherosclerosis the same as age-related atherosclerosis?
• What is the contribution of coronary artery disease (atherosclerosis) versus microvascular damage in radiation induced cardiac damage?
Initiation of age-related atherosclerosis

- Monocyte
- Rolling
- Sticking
- E-selectin
- VCAM-1
- ICAM-1
- MCP-1
- Oxidized LDL
- Foam cell
- Growth factors
- Metalloproteinases
- Cell proliferation
- Matrix degradation

Steps:
1. Monocyte rolling
2. Monocyte sticking
3. Monocyte transmigration
4. Oxidized LDL production
5. Cytokine release

Initiation:
- Monocyte rolling
- Adhesion molecules (E-selectin, VCAM-1, ICAM-1)
- MCP-1
- Oxidized LDL
- Foam cell formation

Vessel lumen
Endothelial cells
Intima
Irradiation of carotid arteries in ApoE-/- mice
(elevated cholesterol levels)

Macrophage rich initial lesion

Advanced lesion with fibrous cap and lipid core
Increased number of lesions in irradiated carotid arteries ApoE-/- mice

No “out of field effects”
Less pronounced effects for 8 Gy than 14 Gy
2 Gy did not increase number of lesions or alter phenotype

Stewart et al. AJP 2006; Hoving et al. IJROBP 2008
Thrombotic phenotype of lesions of irradiated carotid arteries ApoE-/- mice

Activated ECs

Mf + erys

Fibrin deposits

Ruptured media

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

Hoving et al. IJROBP 2008
# Adhesion molecules expressed after irradiation

<table>
<thead>
<tr>
<th>P-selectin</th>
<th>Migration from Weibel-Palade bodies to lumen large pulmonary vessels</th>
<th>Hallahan 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-selectin</td>
<td>↑ mouse large pulmonary vessels</td>
<td>Hallahan 1997</td>
</tr>
<tr>
<td></td>
<td>↑ mouse large pulmonary vessels</td>
<td>Heckmann 1998</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>↑ mouse lung microvasculature</td>
<td>Tsujino 1999; Epperly 2002; Heckmann 1998</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>↑ mouse lung microvasculature</td>
<td>Tsujino 1999; Epperly 2002; Hallahan 1997</td>
</tr>
<tr>
<td></td>
<td>↑ microvessels of skin organ cultures</td>
<td>Heckmann 1998</td>
</tr>
</tbody>
</table>

ICAM1 & VCAM1 decreased in carotid artery of ApoE-/- mice 1 wk after 14 Gy.
MCP1 unchanged after irradiation *(Hoving et al., unpublished)*
Low dose irradiation decreases leukocyte adhesion and inhibits atherosclerosis

- Low dose irradiation of EC decreased leukocyte adhesion \textit{in vitro} via reduced liberation of E-selectin (ICAM1 unchanged)

\textit{Hildebrandt et al., IJRB 2002}

- Low dose TBI inhibits atherosclerosis in aortic root

\textit{Mitchel et al., Rad Res 2011}
Summary of data on radiation-induced atherosclerosis

• Radiation is an independent risk factor for atherosclerosis
• Interaction between high levels of cholesterol and radiation
• Doses ≥8 Gy initiate atherosclerotic processes and predisposes to formation of thrombotic, inflammatory plaques (more likely to rupture and cause fatal event)
• Doses 2 Gy did not stimulate atherosclerosis or alter phenotype (within the 34 week follow-up)
• Doses ≤ 0.5 Gy inhibited atherosclerosis
• Possible involvement of E-selectin in initiation of radiation-induced atherosclerosis?
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)
Acute pericarditis 20-40 weeks after irradiation

Seemann et al., R&O in press
Microvascular changes 40 weeks after RT

Decreased microvascular density

Vascular leakage
- 0 Gy: 20%
- 2 Gy: 50%
- 8 Gy: 100%
- 16 Gy: 91%

Diffuse amyloidosis

Decreased alkaline phosphatase

Fibrosis

Seemann et al., R & O in press
Cardiac function from gated SPECT imaging

Seemann et al. R & O in press

HSA- Tc-99m for blood volume heart chambers

Myoview- Tc-99m for microvascular filling

Lethality in 38% mice between 30-40 weeks after 16 Gy; strongly associated with vascular leakage and amyloidosis
Summary of experimental data on radiation heart damage

- Early, inflammatory changes with restrictive pericarditis
- Microvascular density decreased by 40 weeks after higher doses; functional perfusion of remaining vessels not significantly reduced
- Remaining vessels had reduced alkaline phosphatase and increased vWF, indicative of progressive microvascular damage
- Vascular leakage, diffuse amyloidosis and fibrotic changes from 40 weeks after irradiation is further evidence of the progressive damage
- Endocardial foam cell accumulation and coronary artery lesions from 20 weeks after high doses (ApoE-/- mice only)
- Reduced EDV and ESV from 20 weeks after irradiation, indicative of cardiac remodeling and reduced function
- No further deterioration until shortly before death, indicative of some compensatory mechanisms (upregulation of cardiac β-adrenergic receptors)
Model for development of radiation-induced cardiac damage

Macrovascular injury accelerates age-related atherosclerosis, leading to coronary artery disease (years/decades post-RT)

Microvascular injury reduces capillary density (within months of RT)

**Higher doses**
Reduced flow to a “territory” of myocardium

**Low doses**
Reduced collateral flow/vascular reserve (often subclinical)

Combine to cause myocardial ischemia

*Darby et al., IJROBP 2010*
Study Participants

Ingar Seemann, Saske Hoving, Nils Visser, Hans te Poele, Fijis van Leeuwen, Nicola Russell

Karen Gabriels, Marion Gijbels, Ben Janssen, Sylvia Heeneman, Mat Daemen