Radiation-induced cardiovascular and cerebrovascular damage

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Radiation-induced cardiovascular and cerebrovascular disease

- Epidemiological evidence and dose response relationships
- Experimental models and mechanisms of development of damage
Increased risk of vascular disease mortality in life span study of A-bomb survivors

First observations Kodama and Shimizu 1984

Shimizu et al., Rad Res 2010

Previous estimates ERR 17% (heart disease) and 12% (stroke): Preston et al., 2003
Meta-analysis of risks for circulatory disease after low dose radiation (average heart/brain doses <2.5 Gy)

Little et al., Radiat Environ Biophys 2010

<table>
<thead>
<tr>
<th>A-bomb survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Mortality (Preston 2003)</td>
</tr>
<tr>
<td>- Morbidity (Yamada 2004)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low dose medical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Peptic ulcer study (Carr. 2005)</td>
</tr>
<tr>
<td>- Ankylosing spondylitis (Darby 1987)</td>
</tr>
<tr>
<td>- TB fluoroscopic studies (Davis 1989)</td>
</tr>
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<table>
<thead>
<tr>
<th>Occupational studies</th>
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<tbody>
<tr>
<td>- Canadian workers (Ashmore 1998),</td>
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<tr>
<td>- US Oak Ridge workers (Richardson. 1999)</td>
</tr>
<tr>
<td>- 15-country nuclear workers (Vrijheid 2007)</td>
</tr>
<tr>
<td>- UK NRRW workers (Muirhead 2009)</td>
</tr>
<tr>
<td>- Chernobyl liquidators (Ivanov 2006)</td>
</tr>
<tr>
<td>- Uranium miners (Kreuzer 2006)</td>
</tr>
<tr>
<td>- Mayak workers (Azizova 2010a,b)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environ. studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Three Mile Island study (Talbott 2003)</td>
</tr>
</tbody>
</table>

ERR/Sv (95% CI)

- 0.03 (0.00-0.07)
- 0.08 (0.05-0.11)
- 0.19 (0.14-0.23)

“The epidemiological evidence for an effect of moderate and low doses remains suggestive rather than persuasive”
Radiation as an independent risk factor for cardio- and cerebrovascular 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 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

- Pediatric cranial RT>30 Gy:
  leukemia RR stroke 5.9
  brain tumor RR stroke 38

- H&N cancer patients:
  RR stroke 2.1-5.6
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</th>
<th>Radio. events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Allocated</td>
<td>Allocated</td>
<td>Logrank O-E</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>145/5040</td>
<td>117/4942</td>
<td>4.8</td>
</tr>
<tr>
<td>5 - 15</td>
<td>9</td>
<td>237/4374</td>
<td>170/4476</td>
<td>26.0</td>
</tr>
<tr>
<td>15+</td>
<td>17</td>
<td>125/1140</td>
<td>72/1125</td>
<td>22.7</td>
</tr>
<tr>
<td>Unknown</td>
<td>10</td>
<td>162/5019</td>
<td>157/5045</td>
<td>12.7</td>
</tr>
</tbody>
</table>

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 $0.07$; $2p < 0.00001$

Total

<table>
<thead>
<tr>
<th>Radio. better</th>
<th>Radio. worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>669/15573</td>
<td>516/15588</td>
</tr>
<tr>
<td>(4.3%)</td>
<td>(3.3%)</td>
</tr>
<tr>
<td>66.3 268.5</td>
<td>2p = 0.00005</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*

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*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
Cumulative incidence of stroke in 5-year survivors of childhood leukemia & brain tumors according to dose to major cerebral arteries (n= 6699)

Bowers et al., JCO 2006
Research questions

• Is the etiology of radiation-induced atherosclerosis the same as age-related atherosclerosis?

• Is there an interaction between elevated cholesterol and radiation in development of atherosclerosis?

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

• Is mean heart dose most relevant parameter or is dose distribution to major arteries more important?
Initiation of age-related atherosclerosis

- Monocyte
- Rolling
- Sticking
- Transmigration
- LDL
- Oxidized LDL
- MCP-1
- VCAM-1
- ICAM-1
- E-selectin
- Adhesion molecules
- Cytokines
- Foam cell
- Cell proliferation
- Matrix degradation
- Growth factors
- Metalloproteinases
- Vessel lumen
- Endothelial cells
- Intima
Progression of age-related atherosclerosis

Libby, Nature 2002

- Normal artery
- Early atheroma
- Stabilized advanced plaque
- Vulnerable initial plaque
- Thrombosis of ruptured plaque
Irradiation of carotid arteries in ApoE-/- mice
Cholesterol levels in ApoE-/- and wild type mice

No changes in systemic inflammatory markers

No change in thyroid function (TSH & T4)
Increased incidence of early fatty streaks in irradiated arteries of ApoE-/- mice

<table>
<thead>
<tr>
<th>Follow-up time</th>
<th>0 Gy</th>
<th>14 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week</td>
<td>0/10</td>
<td>0/10</td>
</tr>
<tr>
<td>4 weeks</td>
<td>0/9</td>
<td>4/9 *</td>
</tr>
</tbody>
</table>

Hoving et al., IJROBP 2008
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:

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

- Granulocytes >60% lesions
- Fe containing macrophages >80% lesions
- Fibrin deposits >60% lesions (later times)
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

1 x 2 Gy did not significantly increase number of lesions or change phenotype

Hoving et al., IJROBP 2008
Interaction between hypercholesterolemia and radiation (aortic root lesions)

8 Gy / HFD (C57Bl6 mice)

8 Gy / chow

*Tribble et al., ATVB 1999*
Interaction between hypercholesterolemia and radiation

Aortic lesion size increased with radiation doses 2-8 Gy (repeated measures ANOVA p = 0.02)

*Tribble et al., ATVB 1999*
# Inflammatory markers 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>↑ microvessels of skin organ cultures</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></td>
<td>↑ microvessels of skin organ cultures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ microvessels of skin organ cultures</td>
<td></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)*
Atherosclerotic lesions in aortic root after low dose total body irradiation of ApoE-/- mice

Courtesy Guido Hildebrandt
NOTE consortium, December 2010
Low dose TBI decrease number and size of lesions

Mitchel et al., Rad Res 2011

But: lesions more severe
Low dose irradiation decreases leukocyte adhesion in vitro and in vivo

- Low dose irradiation decreased early leukocyte adhesion to EC via decreased liberation of E-selectin, no modification ICAM1 (Hildebrandt et al., IJRB 2002)

- Low dose abdominal irradiation decreased LPS-induced leukocyte rolling and adhesion in colonic venules via stimulated release of TGFβ, no modification of ICAM1 levels (Arenas et al., IJROBP 2006)
Summary of data on radiation-induced atherosclerosis

- Radiation is an independent risk factor for atherosclerosis.
- Interaction between high levels of cholesterol and radiation.
- Doses $\geq 8$ Gy initiate atherosclerotic processes and predispose to formation of thrombotic, inflammatory plaques (more likely to rupture and cause fatal event) in carotid artery.
- Doses $2-8$ Gy in combination with high cholesterol diet increased atherosclerotic plaque in aortic root.
- Doses $\leq 0.5$ Gy inhibited atherosclerosis.
- Possible involvement of E-selectin in initiation of radiation-induced atherosclerosis?
Manifestations and pathogenesis of radiation induced cardiovascular damage

- **EC:** thrombotic and inflammatory cytokines, cell loss *(days/weeks)*
- **Capillary network:** obstruction, decreased MVD, perfusion defects, myocardial degeneration and fibrosis *(weeks/months)*
- **Medium vessels:** intimal thickening, perivascular fibrosis *(weeks/months)*
- **Pericardium:** pericarditis *(months)*
- **Myocardium:** reduced systolic function, valve defects *(months)*
- **Large arteries:** atherosclerosis, stenosis, stroke, MI *(years)*
- **Valves:** thickening, fibrosis and cacification *(>10 years)*
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
(C57Bl6 mice only)

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

No significant changes at 20 weeks

Effects more pronounced and earlier in ApoE-/- mice

Seemann et al., R&O in press
Microvascular changes 40 weeks after RT
(Effects more pronounced and earlier in ApoE-/- mice)

Seemann et al., R & O in press
**Microvascular leakage at 40 weeks after RT**

*Seemann et al., R & O in press*

<table>
<thead>
<tr>
<th></th>
<th>mild deposition</th>
<th>strong deposition</th>
<th>any deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>20 weeks Follow up</strong></td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>40 weeks Follow up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 Gy</td>
<td>1/5</td>
<td>0/5</td>
<td>1/5</td>
</tr>
<tr>
<td>2 Gy</td>
<td>4/8</td>
<td>0/8</td>
<td>4/8</td>
</tr>
<tr>
<td>8 Gy</td>
<td>8/8</td>
<td>0/8</td>
<td>8/8</td>
</tr>
<tr>
<td>16 Gy total</td>
<td>5/11</td>
<td>5/11</td>
<td>10/11</td>
</tr>
</tbody>
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*Hearts with strong albumin protein deposition also had diffuse amyloidosis*
TBI but not local thoracic irradiation (10 Gy) induces hypercholesterolemia

Baker et al., IJRB 2010
TBI gives greater vascular damage than local thoracic irradiation in rats (10 Gy)

- Decreased density of small coronary arterioles 120 days after 10 Gy TBI but no change after thoracic irradiation

- Myointimal proliferation and sclerosis blocking mid-sized coronary vessels after TBI only (120 days)

- Effects possibly secondary to renal damage, proteinuria and hypertension

Baker et al., IJRB 2010
Cardiac function from gSPECT imaging after thoracic irradiation

HSA- Tc-99m for blood volume heart chambers

Myoview- Tc-99m for microvascular filling

Seemann et al., R&O in press
gSPECT myoview: heart function
(both strains)

20 weeks

Lethality in 38% C57Bl6 mice at 30-40 weeks after 16 Gy; strongly associated with vascular leakage and amyloidosis

Seemann et al., R&O in press
Heart damage in rats after local irradiation (20 Gy/1 year)

- Decreased cardiac output (to 50% control) parallels focal myocardial degeneration

- Further reduction in CO only seen immediately before congestive heart failure

- Compensatory mechanisms (upregulation of cardiac $\beta$-adrenergic receptors) maintain steady state for many weeks

Schultz-Hector et al., Rad Res 1992
Ex vivo working heart model

No interference from compensatory mechanisms (circulation, CNS)

Courtesy Marjan Boerma
DoReMi, December 2010
Comparison of cardiac function *in vivo* with *ex vivo* cardiac performance after 20 Gy

- Compensatory mechanisms maintain heart function *in vivo* until shortly before death
- More rapid and progressive deterioration in *ex vivo* cardiac performance

*Franken et al., BJR 1997*
Early, inflammatory changes with restrictive pericarditis (C57Bl6 mice)

- 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 (C57Bl6 mice) is further evidence of the progressive damage
- Endocardial foam cell accululation 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 in both strains
- No further deterioration of function until shortly before death (after high doses), indicative of some compensatory mechanisms

Summary of experimental data on radiation heart damage
Prospective evaluation of perfusion defects after RT for left sided breast cancer

- Progressive increase in perfusion defects greatest when >5% LV in RT field
- Defects follow contour of RT field rather than coronary arteries
- Wall motion abnormalities in LV correlated with perfusion defects

<table>
<thead>
<tr>
<th>FU time (months)</th>
<th>Wall motion abnormalities</th>
<th>Wall motion abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No perfusion defects</td>
<td>With perfusion defects</td>
</tr>
<tr>
<td>6</td>
<td>4/53 (7.5%)</td>
<td>8/20 (40%*)</td>
</tr>
<tr>
<td>12</td>
<td>2/39 (5.1%)</td>
<td>2/16 (12.5%)</td>
</tr>
<tr>
<td>24</td>
<td>0/14 (0%)</td>
<td>3/11 (27.3%*)</td>
</tr>
</tbody>
</table>

Marks et al. IJROBP 2005
Research questions

• Is the etiology of radiation-induced atherosclerosis the same as age-related atherosclerosis?  **No**

• Is there an interaction between elevated cholesterol and radiation in development of atherosclerosis?  **Yes**

• What is the contribution of coronary artery disease (atherosclerosis) versus microvascular damage in radiation induced cardiac damage?  **Both important**

• Is mean heart dose most relevant parameter or is dose distribution to major arteries more important?  **?**
Model for development of radiation induced cardiac damage

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

Higher doses
Reduced flow to a “territory” of myocardium

Microvascular injury reduces capillary density (within months of RT)

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,
Fijs van Leeuwen, Nicola Russell

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