Mechanisms and dose response relationship for radiation-induced cardiovascular damage

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- Epidemiological evidence and dose response relationships from irradiated cancer patients

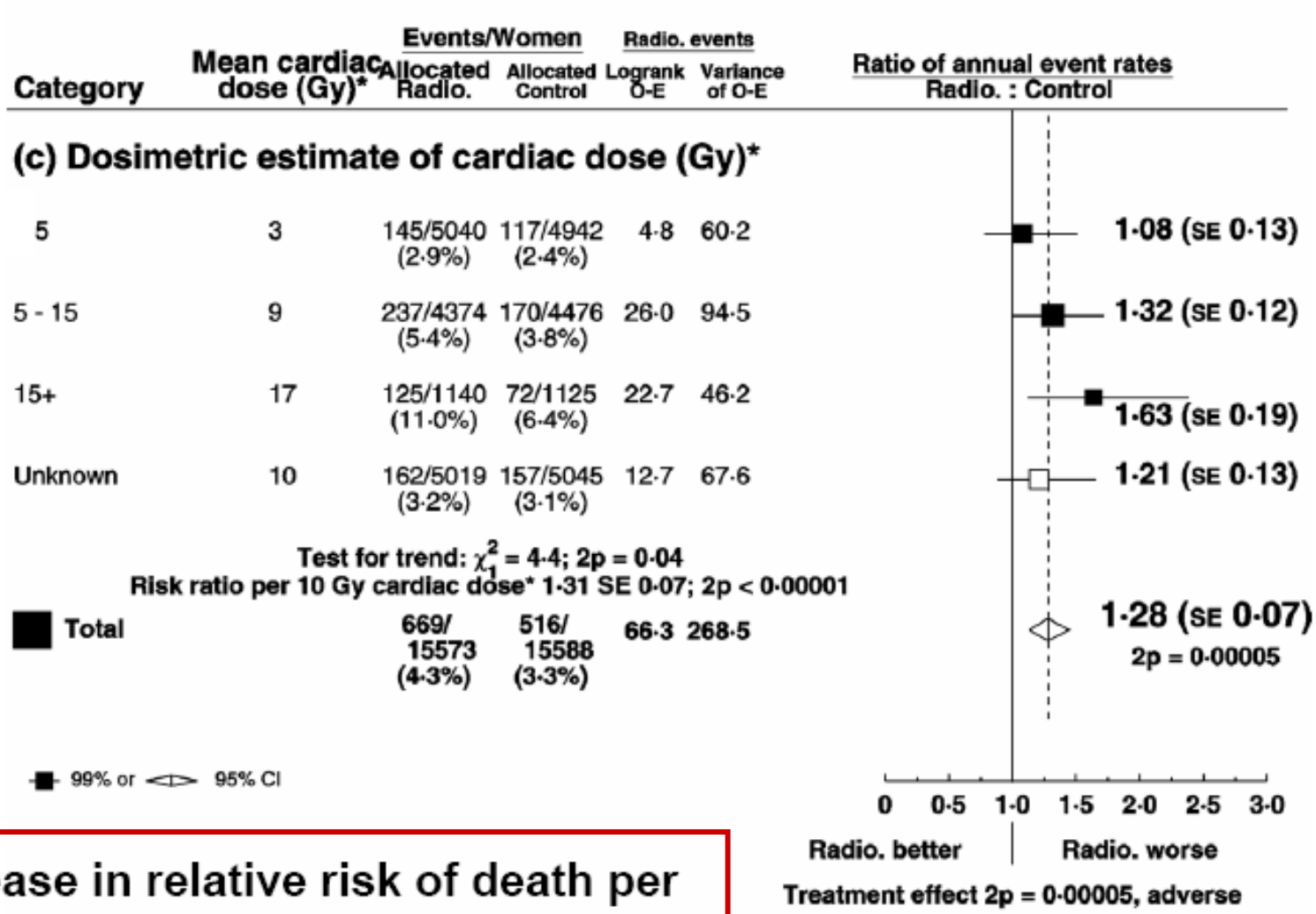
- Experimental models and mechanisms of development of damage

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 anlaysis 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

Risks for cardiac death in women randomized to receive RT vs no RT for breast cancer



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

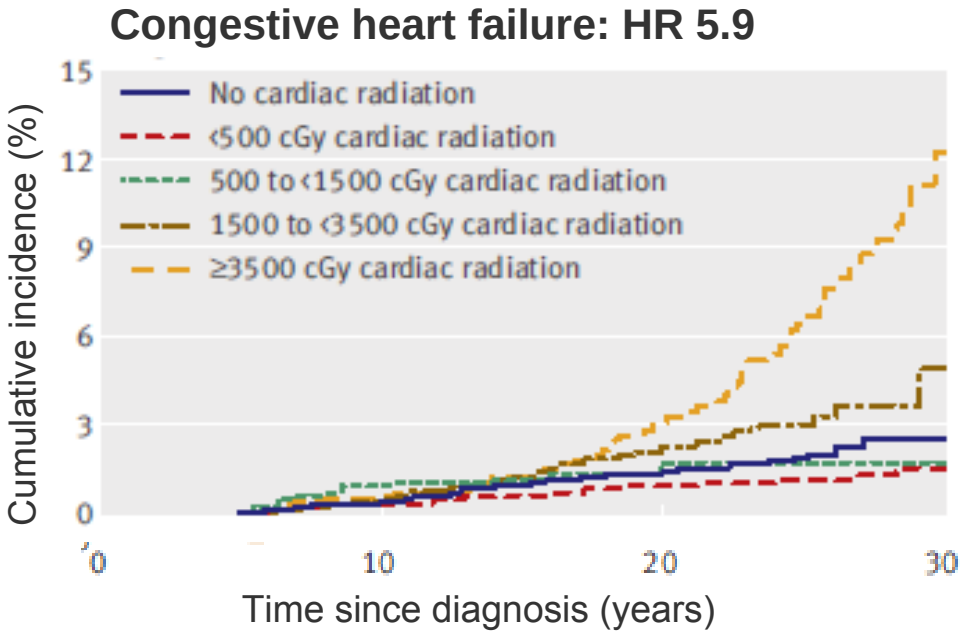
- 72,134 women diagnosed with breast cancer (1976-2006)
- 34,825 (48%) received radiotherapy
- Mean heart dose 6.3 Gy for left and 2.7 Gy for right-sided tumors
- Mean dose LADCA ≥15 Gy for left and 1-2 Gy for right-sided tumors

Disease type	Incidence ratio (L/R)	p-value
Myocardial infarct	1.22	0.007
Angina	1.25	0.01
Pericarditis	1.61	0.03
Valvular disease	1.70	0.009
All heart disease	1.08	0.01

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)



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%

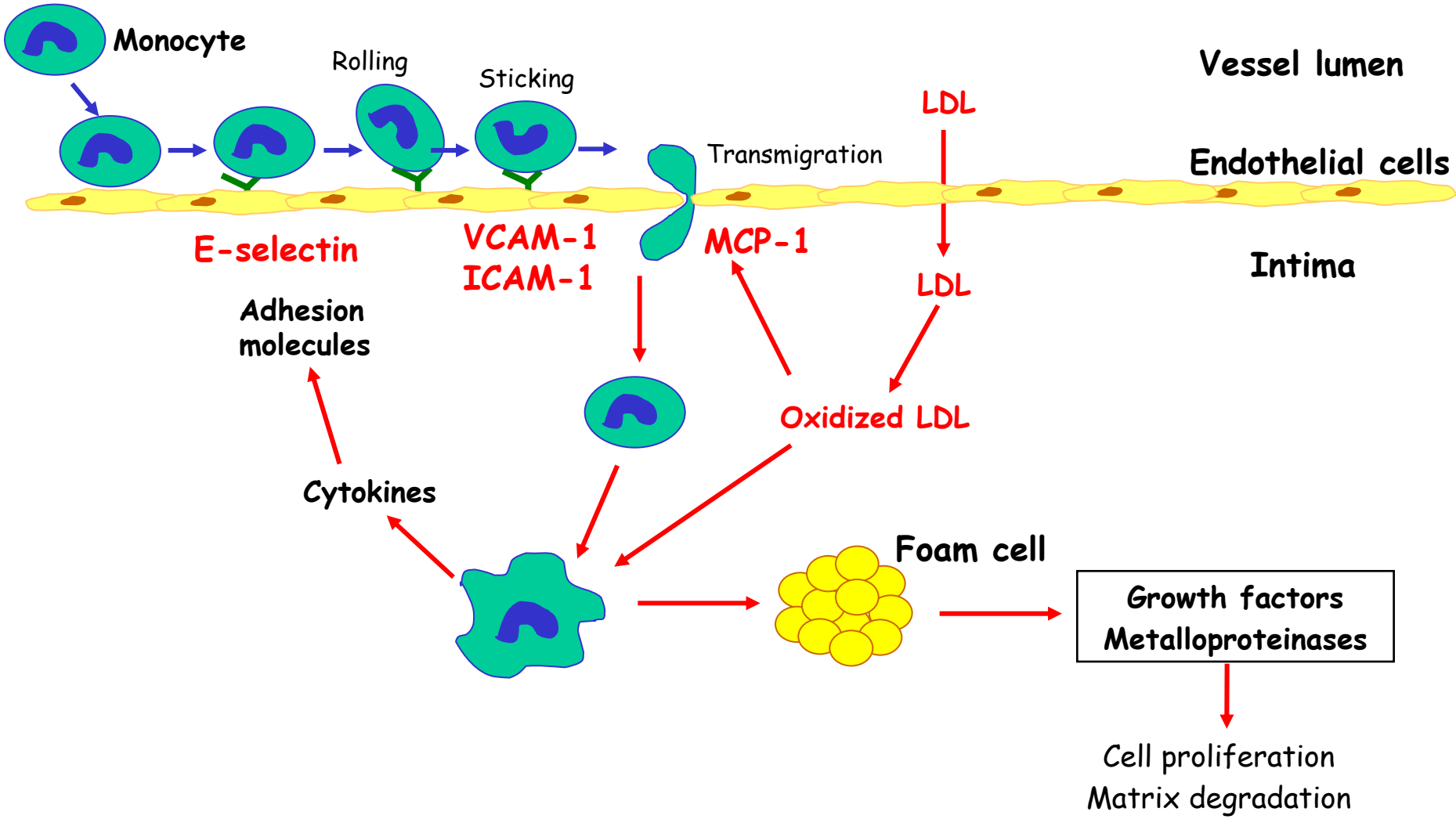
Mean heart dose (Gy)	No of patients	RR CVD mortality
None	1252	1
<1.0	1243	3.0 (0.3-28)
1-5	508	2.5 (0.2-41.5)
5-15	**421**	**12.5 (1.4-116.1)**
>15	**541**	**25.1 (3.0-209.5)**

Tukenova et al., JCO 2010

Research questions

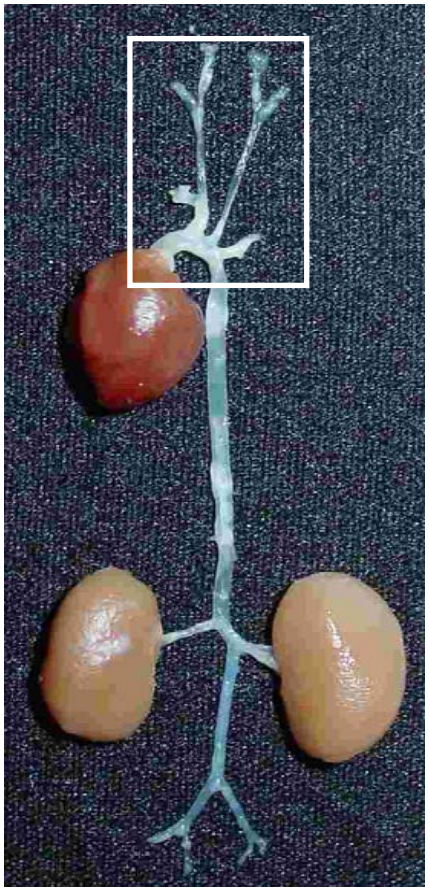
- Is the etiology of radiation-induced atherosclerosis the same as age-related atherosclerosis?
- What is the contribution of coronary artery disease (atherosclerosis) versus microvascular damage in radiation induced cardiac damage?

Initiation of age-related atherosclerosis

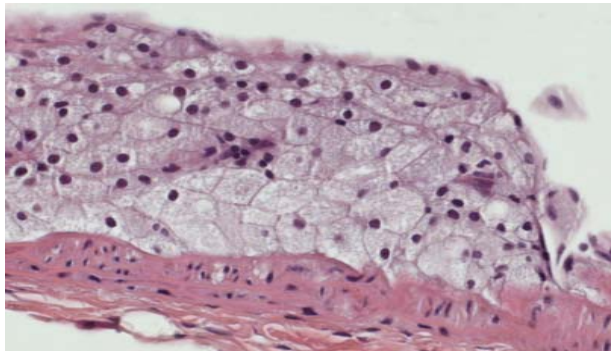


Irradiation of carotid arteries in ApoE-/- mice

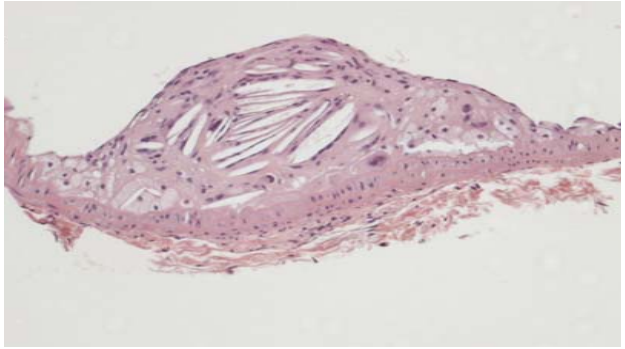
(elevated cholesterol levels)



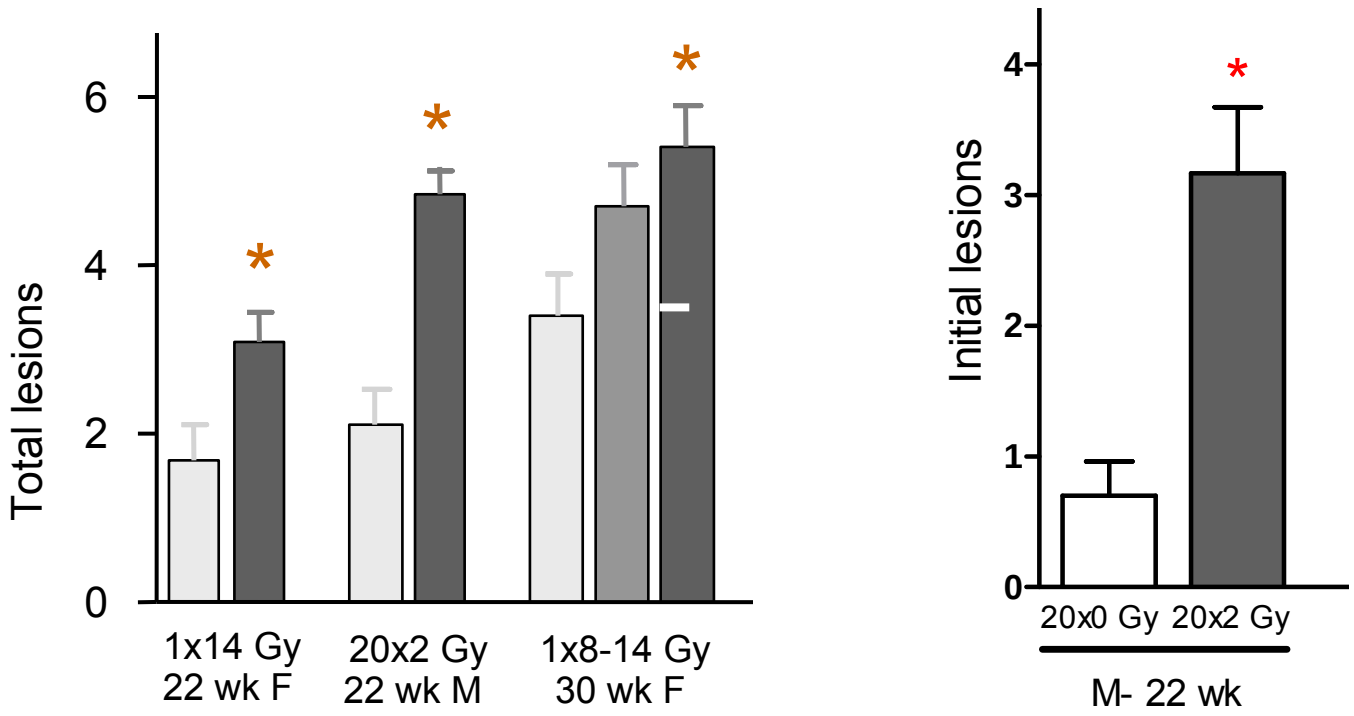
Macrophage rich initial lesion



Advanced lesion with fibrous cap and lipid core



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



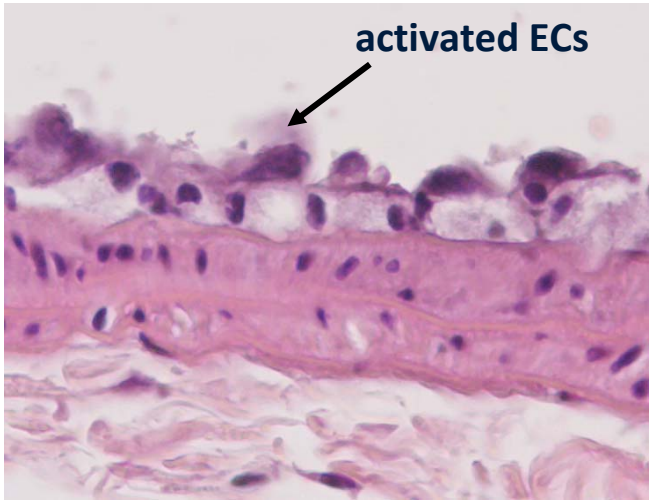
No “out of field effects”

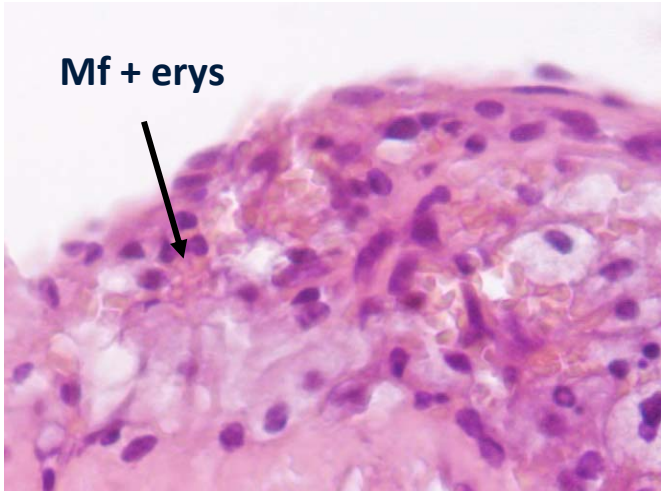
Less pronounced effects for 8 Gy than 14 Gy

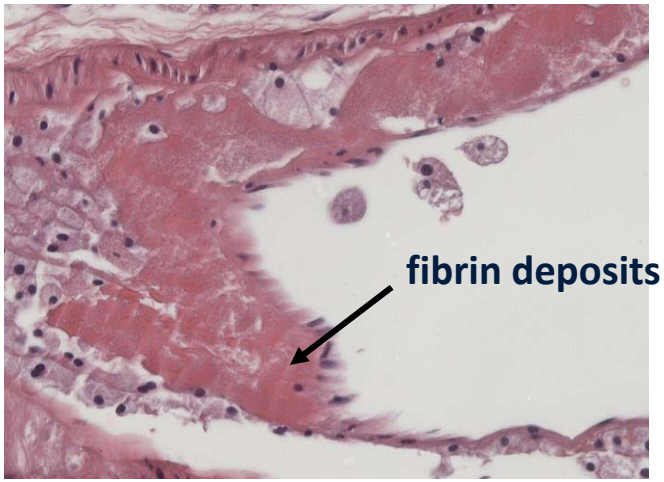
2 Gy did not increase number of lesions or alter phenotype

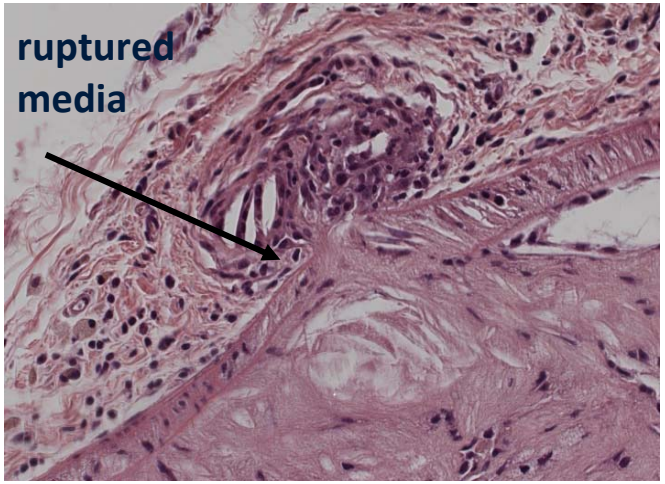
Stewart et al. AJP 2006; Hoving et al. IJROBP 2008

Thrombotic phenotype of lesions of irradiated carotid arteries ApoE-/- mice



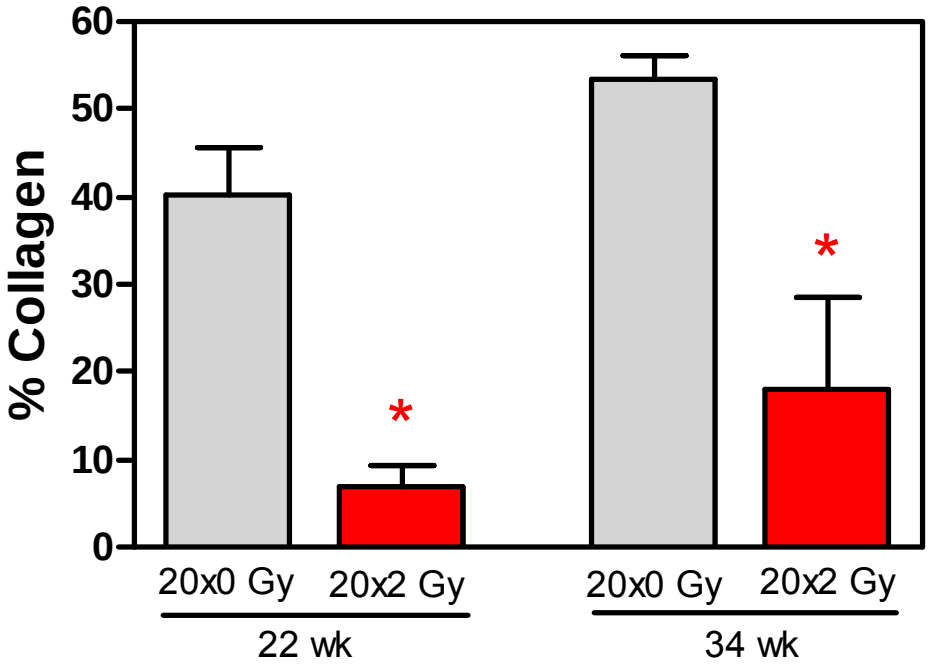


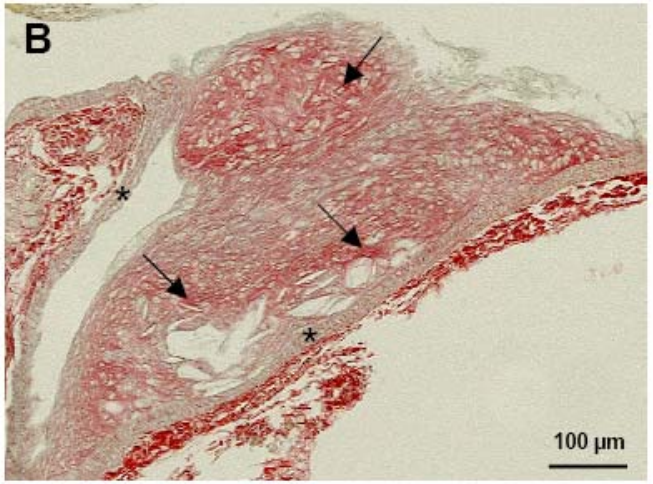


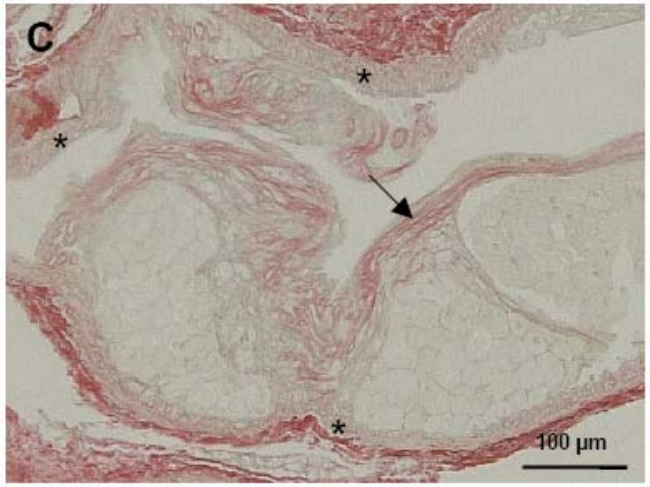


Stewart et al., AJP 2006; Hoving et al., IJROBP 2008

Decreased collagen content in irradiated advanced lesions







Hoving et al. IJROBP 2008

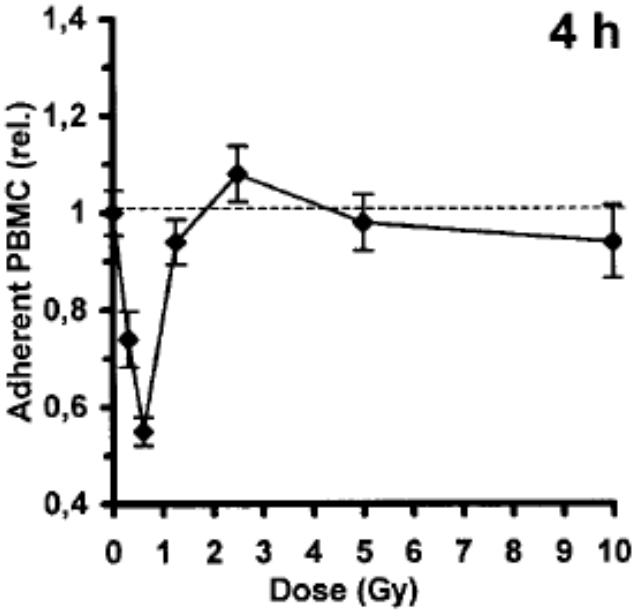
Adhesion molecules expressed after irradiation

P-selectin	**Migration from Weibel-Palade bodies to lumen large pulmonary vessels**	Hallahan 1997
E-selectin	↑ **mouse large pulmonary vessels** ↑ microvessels of skin organ cultures	Hallahan 1997 Heckmann 1998
VCAM-1	↑ mouse lung microvasculature ↑ microvessels of skin organ cultures	Tsujino 1999; Epperly 2002 Heckmann 1998
ICAM-1	↑ mouse lung microvasculature ↑ microvessels of skin organ cultures	Tsujino 1999; Epperly 2002; Hallahan 1997 Heckmann 1998

ICAM1 & VCAM1 decreased in carotid artery of ApoE-/- mice 1 wk after 14 Gy

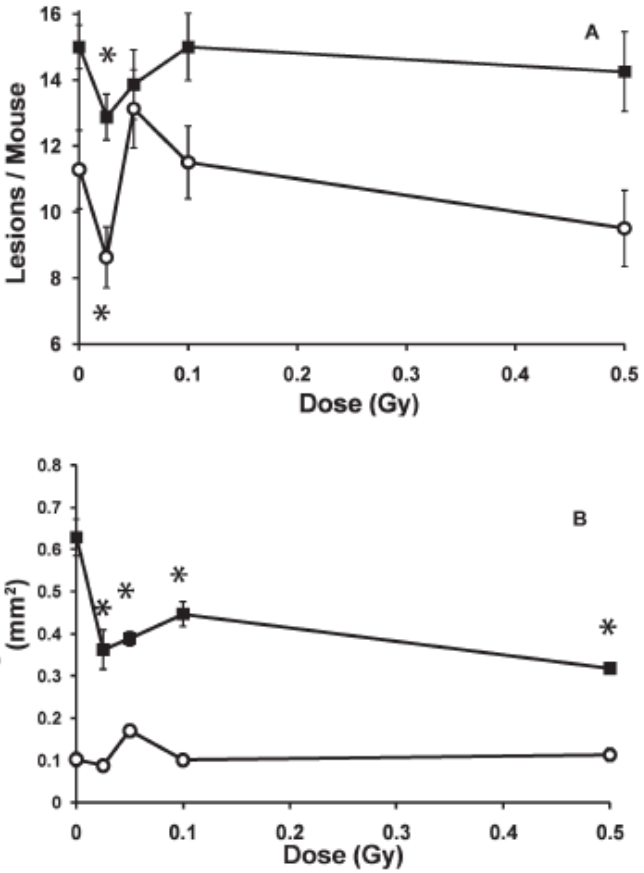
MCP1 unchanged after irradiation ***(Hoving et al., unpublished)***

Low dose irradiation decreases leukocyte adhesion and inhibits atherosclerosis



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

Hildebrandt et al., IJRB 2002



- Low dose TBI inhibits atherosclerosis in aortic root

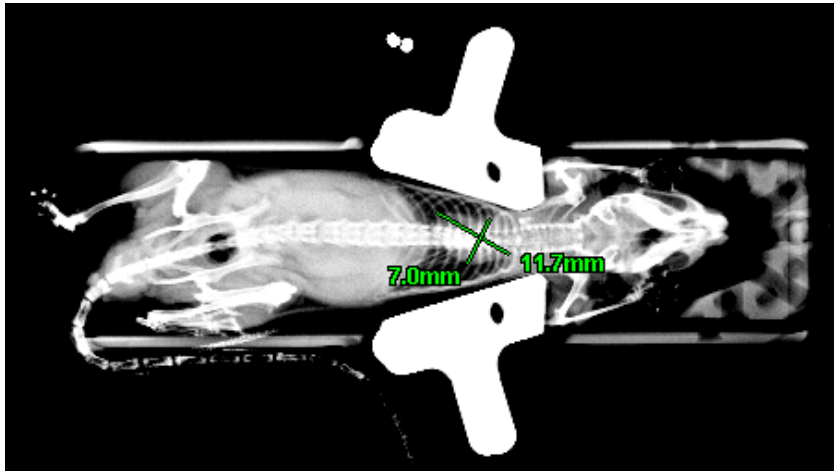
Mitchel et al., Rad Res 2011

Summary of data on radiation-induced atherosclerosis

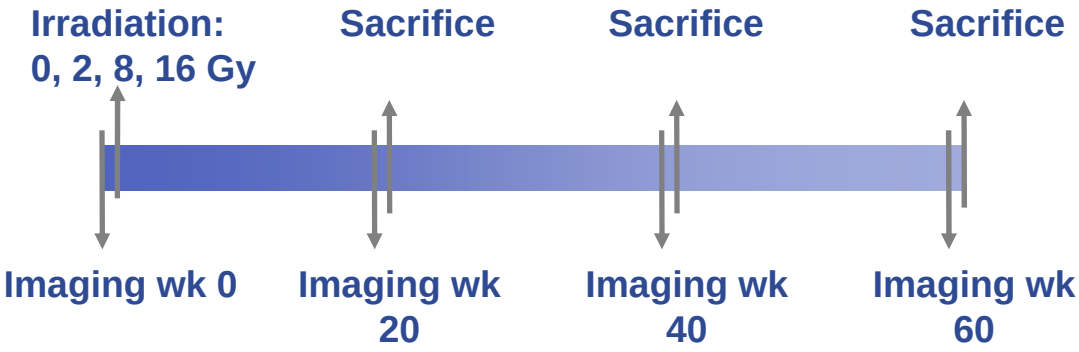
- Radiation is an independent risk factor for atherosclerosis
- Interaction between high levels of cholesterol and radiation
- Doses ≥8 Gy initiate atherosclerotic processes
and predisposes to formation of thrombotic, inflammatory plaques (more likely to rupture and cause fatal event)
- Doses 2 Gy did 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

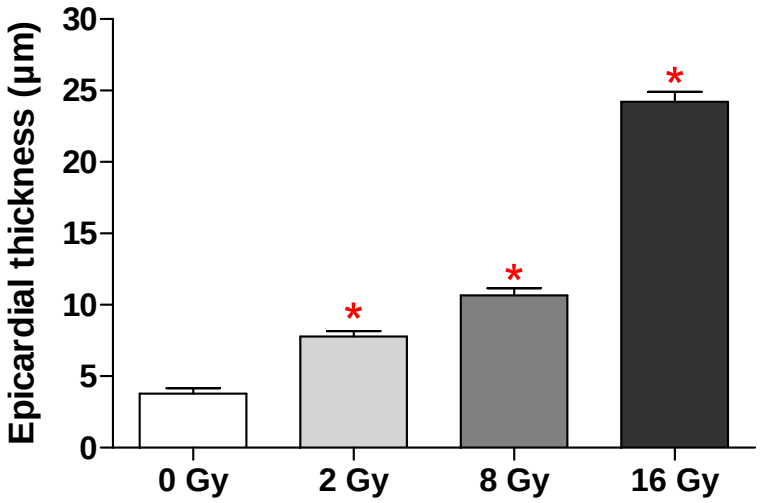
Wild type male C57Bl6 mice; ApoE-/- mice (elevated cholesterol levels)

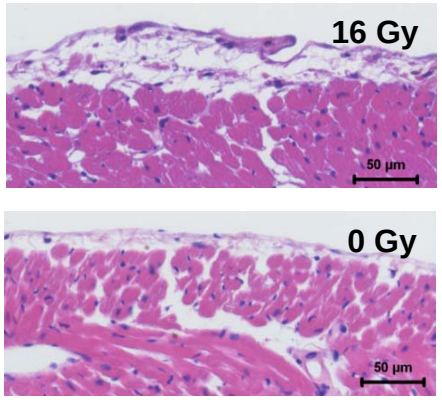


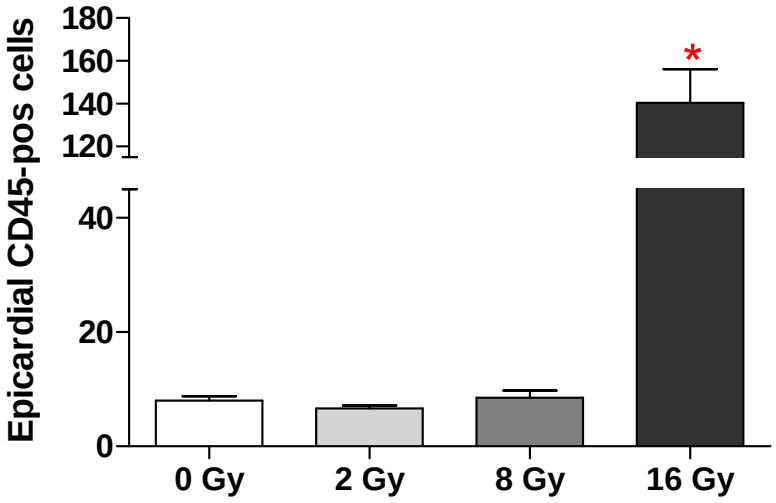
Allowing for margins and individual anatomical variation:
10.6 x 15.0 mm field
(33% lung in field)



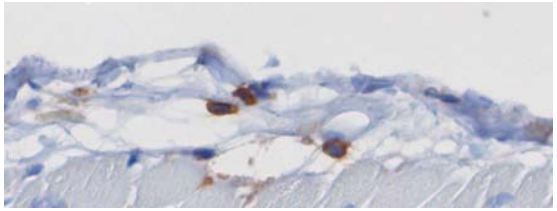
Acute pericarditis 20-40 weeks after irradiation



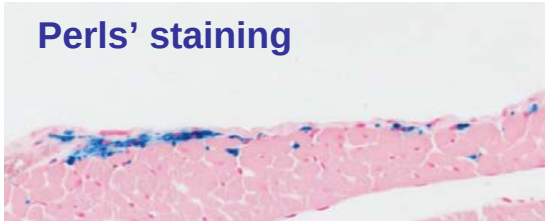




CD45 staining



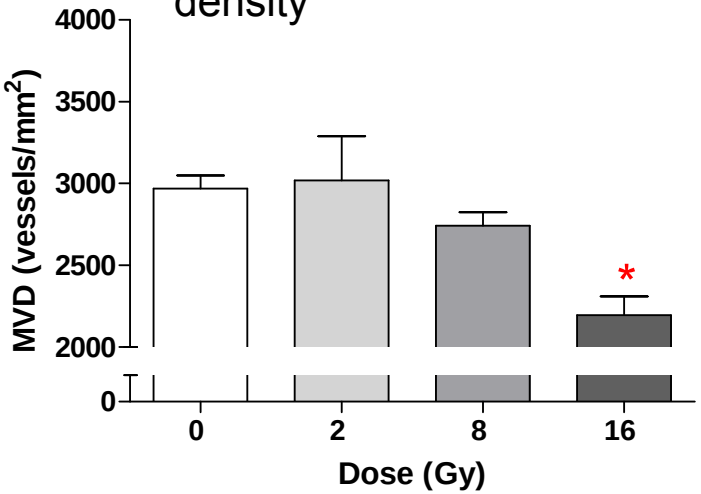
Perls' staining



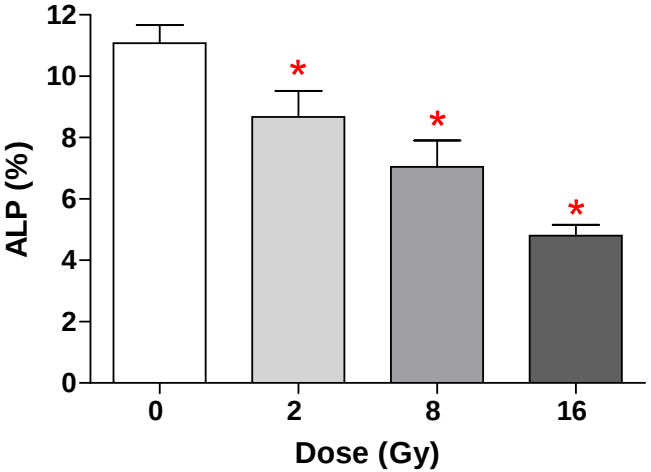
Seemann et al., R&O in press

Microvascular changes 40 weeks after RT

Decreased microvascular density



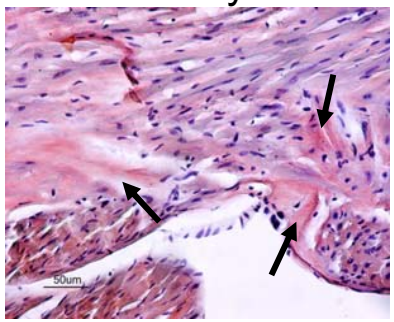
Decreased alkaline phosphatase



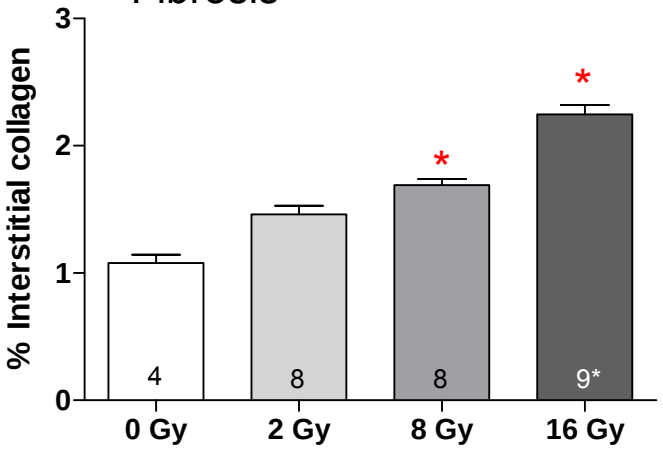
Vascular leakage

0 Gy	20%
2 Gy	50%
8 Gy	100%
16 Gy	**91%**

Diffuse amyloidosis



Fibrosis

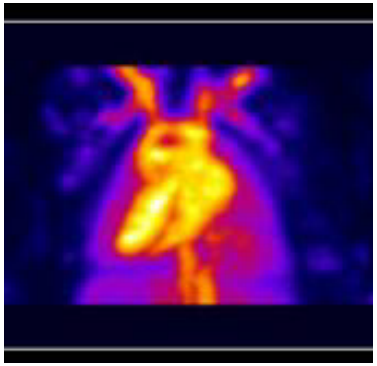


Seemann et al., R & O in press

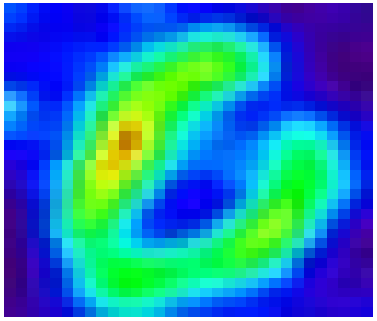
Cardiac function from gated SPECT imaging

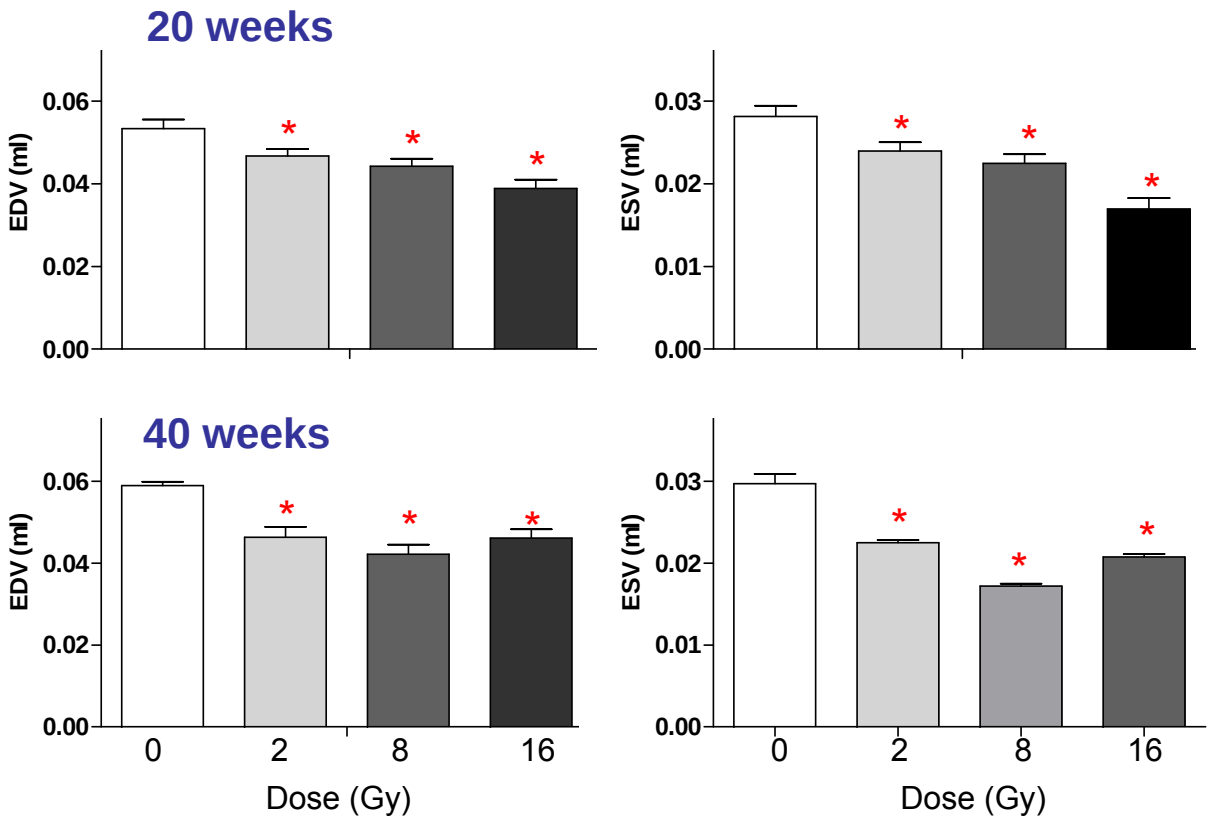
Seemann et al. R & O in press

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 acculation 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 cadiac 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

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DUTCH CANCER SOCIETY

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CARDIO RISK