Advances and Challenges in Radiation Protection of Patients

Cardiovascular risks in radiotherapy

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- University College London

Death from cardiovascular disease in patients treated with radiotherapy for Hodgkin´s disease

Aleman et al., J.Clin.Oncol. 21:3431-3439 (2003)

Age at therapy	observed	expected	RR
< 20 (n=329)	6	0.4	15
21–30 (n=582)	18	2.5	7
31-40 (n=350)	21	4.3	5

Patients and methods: dose reconstruction

n=55 long-term survivors

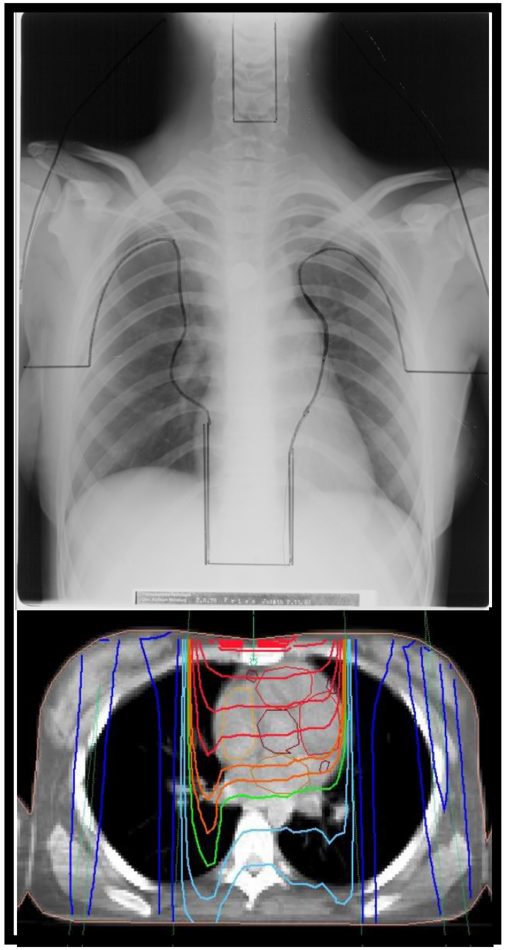
Treatment period 1978-85

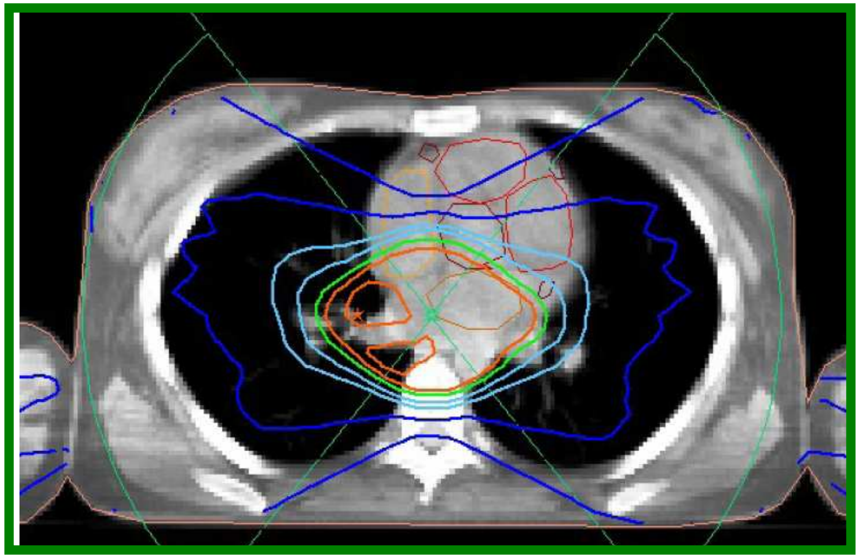
Mean age at time of treatment: 25 (6-49) years

60% RT alone, 40% RT + ChT

45% anterior mantle field (mean dose 36.7 Gy)

33% anterior mantle field + boost (mean dose 41.7 Gy)





(Vordermark et al., Radiat Oncol 2006)

Patients and methods: dose reconstruction

	Maximum dose to cardiac structure	
	MF n=26	**MF+ROT n=18**
RV max	**49 (23-58)**	**48 (43-58)**
LV max	**46 (12-53)**	**45 (18-55)**
LA max	**38 (18-46)**	**45 (36-49)***
RA max	**47 (21-55)**	**49 (42-57)**
RCA max	**48 (22-56)**	**46 (40-56)**
LAD max	**39 (9-55)**	**44 (16-50)**
LCX max	**34 (16-43)**	**42 (19-46)***

Results: overview of pathologic findings

25 patients with complete MRI data

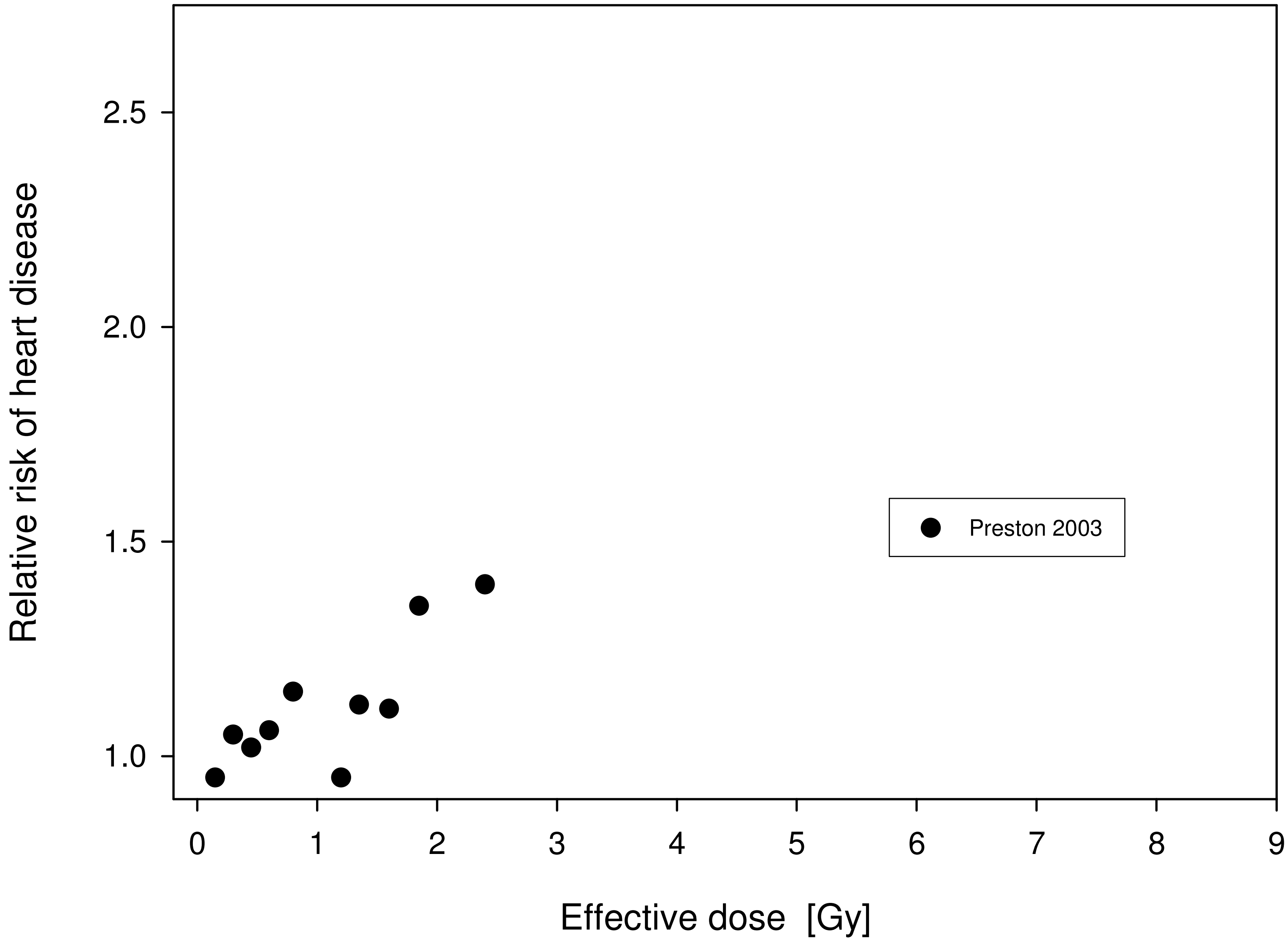
Perfusion deficit at rest →	**16/25 (64%)**
Perfusion deficit under stress only	**1/25 (4%)**
Old infarction („late enhancement“)	**9/25 (36%)**
Reduced ejection fraction (<55%)	**7/25 (28%)**
Valvular changes	**8/25(32%)**
Pericardial effusion	**5/25 (20%)**

A bomb survivors life span study
Non-cancer mortality

Preston et al., Radiation Research 160:381-407 (2003)

Deaths 1968 - 1997

Deaths from non-cancer cause	14459
Deaths from heart disease	4477
Heart deaths attributable to radiation exposure	101



Relative risk of heart disease
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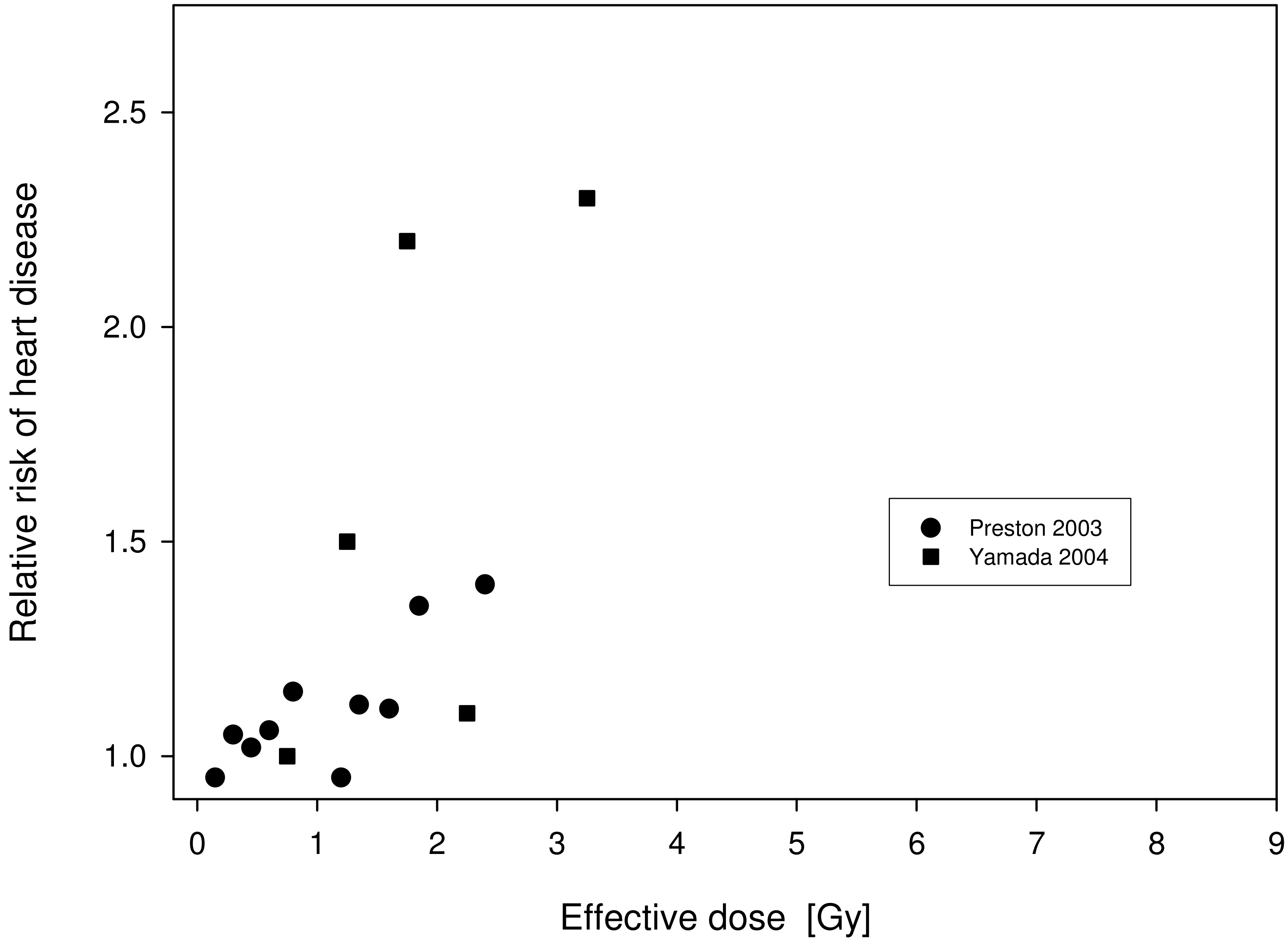
Effective dose [Gy]
Preston 2003



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Effective dose [Gy]
Preston 2003
Yamada 2004

Coronary heart disease after radiotherapy for peptic ulcer disease

Carr et al. Int.J.Radiat.Oncol.Biol.Phys. 61:842-850 (2005)

1859 patients treated with radiotherapy

Compared with

1860 patients treated with drugs

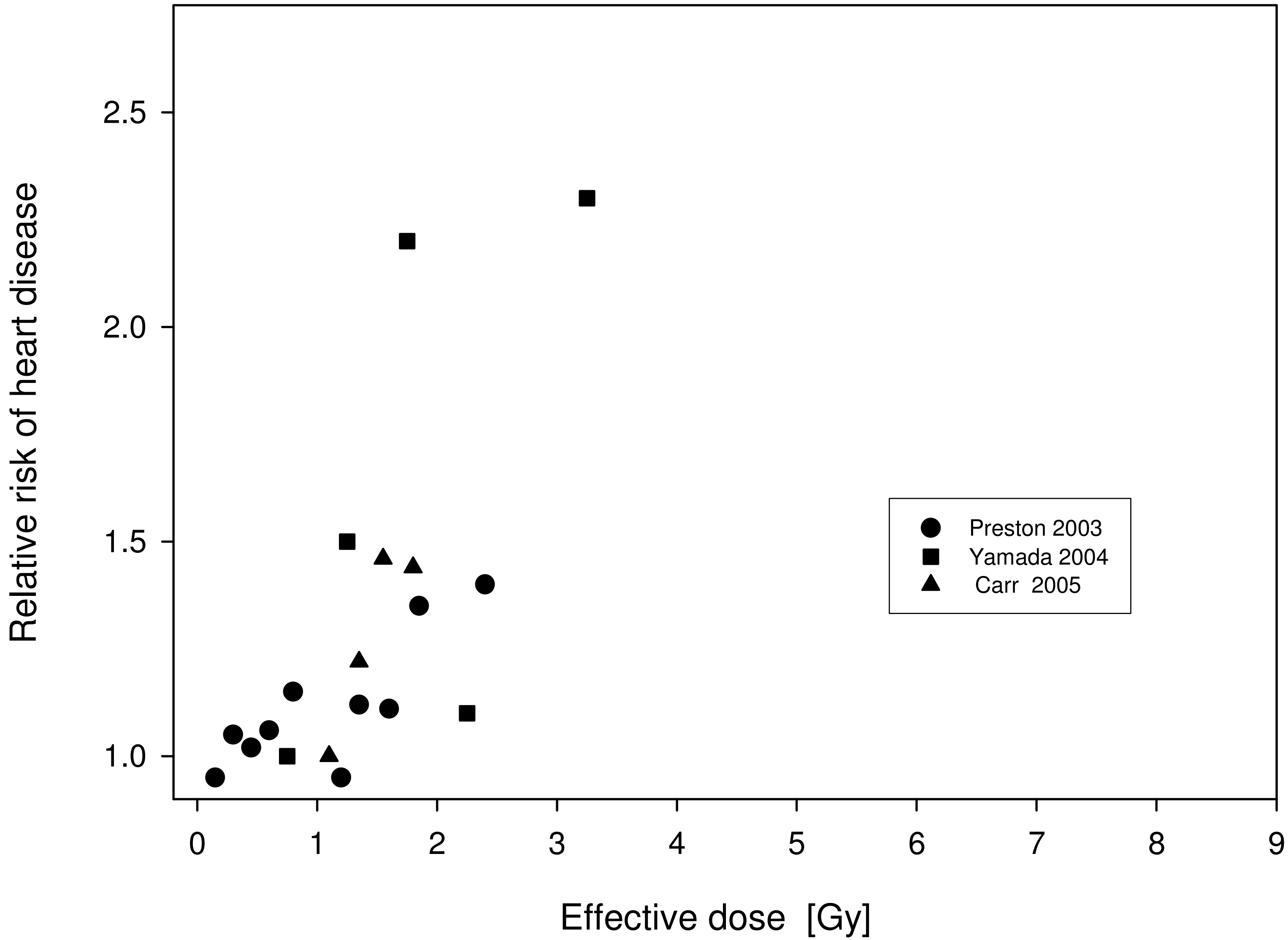
Doses to the stomach were 8 – 18 Gy in fractions of 1.5 Gy

Mean doses to the heart were 1.6 – 3.9 Gy in fractions of 0.33 Gy

Dose dependence of radiation-induced cardiovascular deaths

Carr et al. 2005

Heart dose	*eqsd*	patients	cv deaths	RR
0 Gy	*0*	1568	484	1.0
1.6 Gy	*1.2*	363	94	1.0
2.3 Gy	*1.4*	384	97	1.23
2.8 Gy	*1.7*	341	114	1.54
3.9 Gy	*2.2*	382	121	1.51



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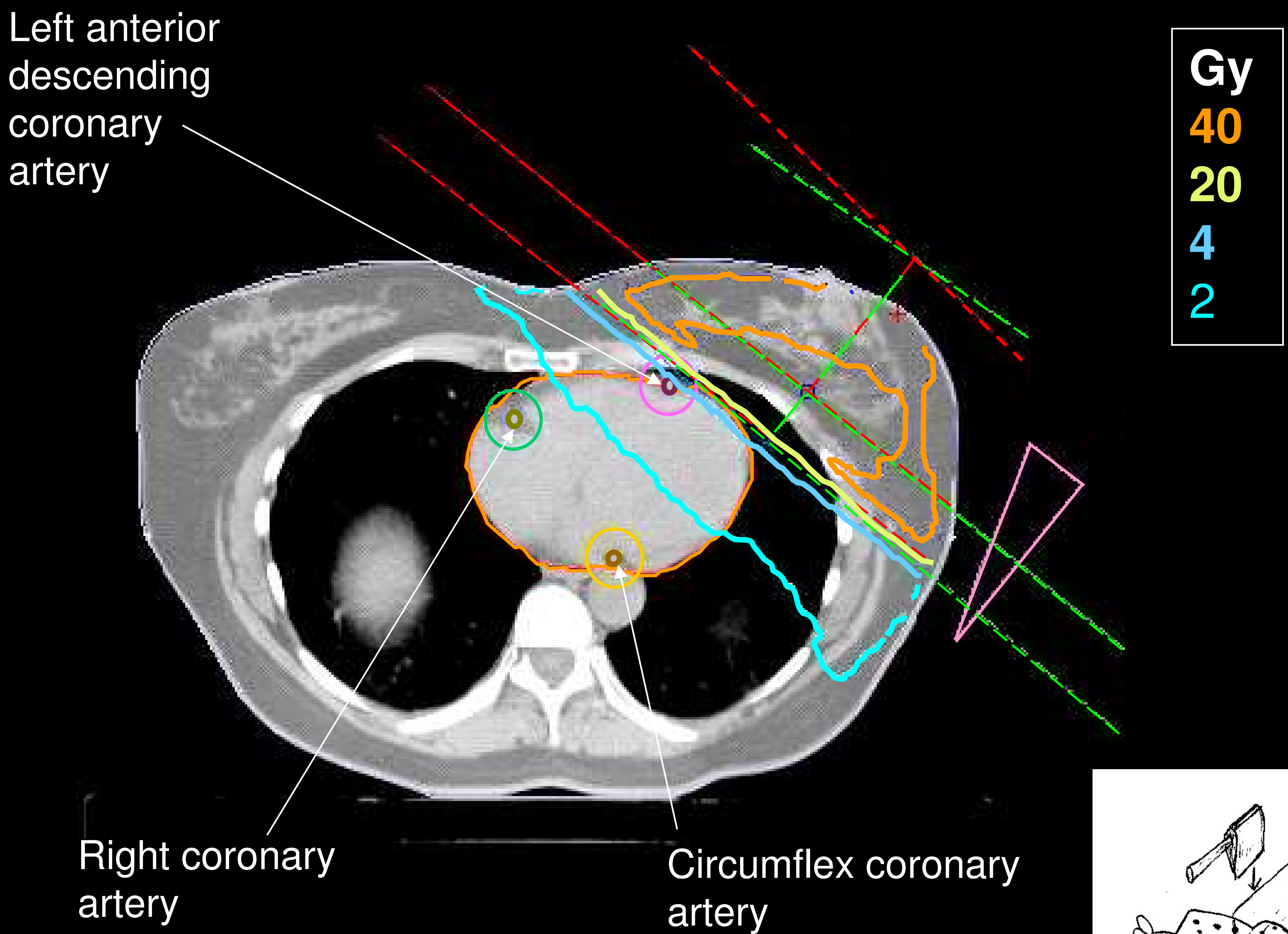
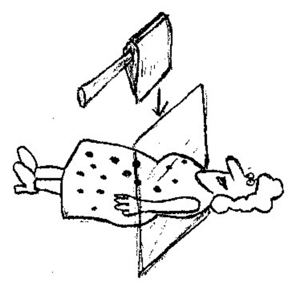
Effective dose [Gy]
Preston 2003
Yamada 2004
Carr 2005

Left breast irradiation in the year 2006*





Taylor et al Int J Radiat Oncol Biol Phys 2008

The risk of cardiovascular disease after radiotherapy
Darby, S.C. et al. Lancet Oncology 6: 557-565 (2005)

Study design:

308,861 women included in the Surveillance, Epidemiology and End Results (SEER) programme who were treated for breast cancer between 1973 and 2001. 115,165 (37%) had received radiotherapy as part of primary treatment.

Endpoint:

dependence of death from cardiovascular disease on laterality of breast cancer.

Results:

1. **Of those 4,130 women who died after >10 years, 1,721 (42%) died from breast cancer, but 894 (22%) died from heart disease.**
2. **Postoperative radiotherapy of left sided breast cancer was associated with a 44% higher risk of death from cardiovascular disease compared to right sided breast cancer.**
3. **Mortality from radiation-induced heart disease increased with time after radiotherapy.**

SEER study by Darby 2005:

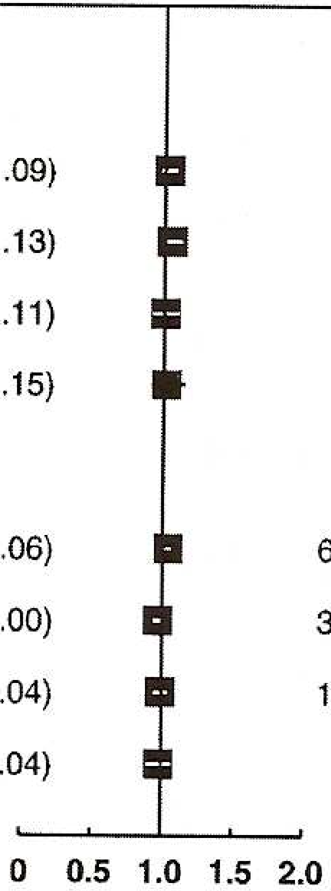
Results of the patient group with >20 years follow-up:

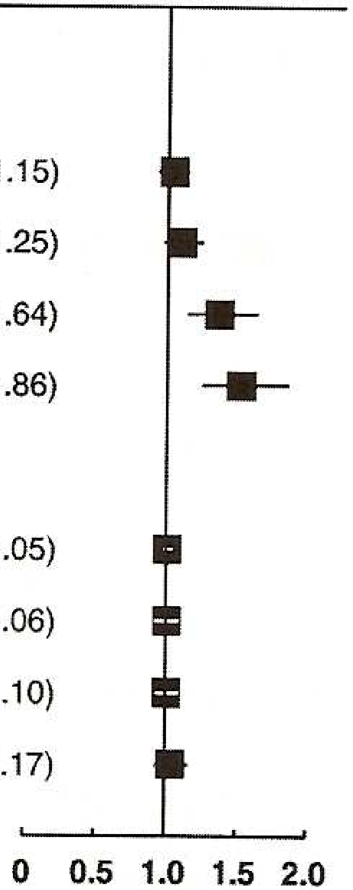
time after diagnosis	cardiac deaths		mortality ratio
years	left	right	
< 5	230	180	1.19
5 – 9	189	145	1.21
10 – 14	157	106	1.42
> 15	234	145	1.58

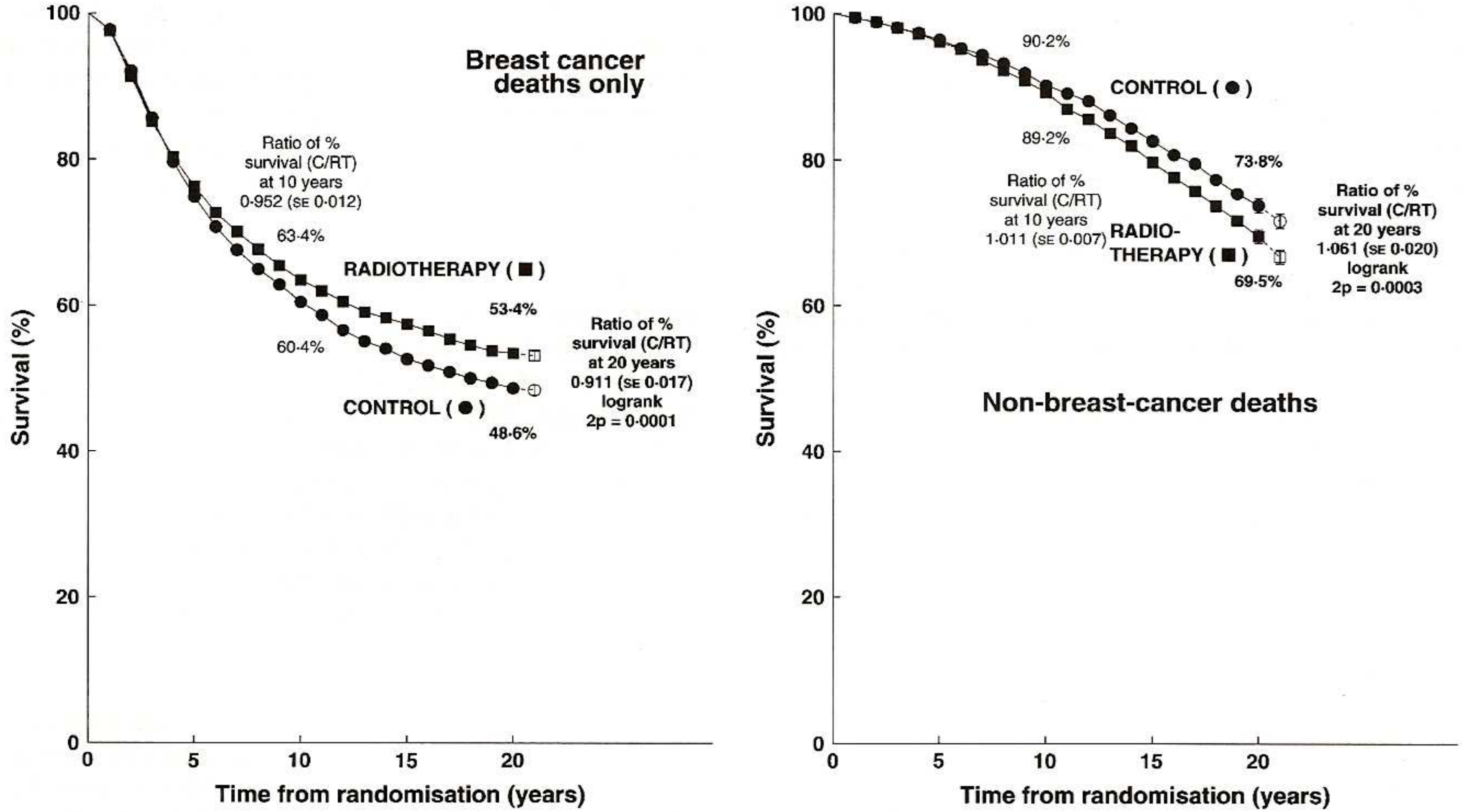
There is, as yet, no convincing evidence that cardiovascular risk in the group treated in the eighties is reduced due to improved technique

Figure 1: Left- versus right-sided breast cancer: subsequent mortality ratios by radiotherapy status, cause, and years since diagnosis in 300 000 women with breast cancer and registered with the SEER cancer registries (based 17).

Years since breast cancer diagnosis	No radiotherapy		Radiotherapy	
	No. of deaths left/right	Mortality ratio left versus right & 95% CI	No. of deaths left/right	Mortality ratio left versus right & 95% CI
Heart disease death				
< 5 years	2164/1972	1.03 (0.97-1.09)	700/633	1.04 (0.93-1.15)
5 - 9	1632/1479	1.05 (0.98-1.13)	521/442	1.10 (0.97-1.25)
10 - 14	806/758	1.01 (0.91-1.11)	281/197	1.37 (1.14-1.64)
15+	568/524	1.02 (0.91-1.15)	254/162	1.53 (1.25-1.86)
All other known causes				
< 5 years	14775/13522	1.04 (1.01-1.06)	6911/6516	1.01 (0.98-1.05)
5 - 9	8009/7863	0.97 (0.94-1.00)	3178/2990	1.01 (0.96-1.06)
10- 14	3472/3343	0.99 (0.94-1.04)	1165/1095	1.01 (0.93-1.10)
15+	2106/2040	0.98 (0.92-1.04)	611/560	1.04 (0.93-1.17)







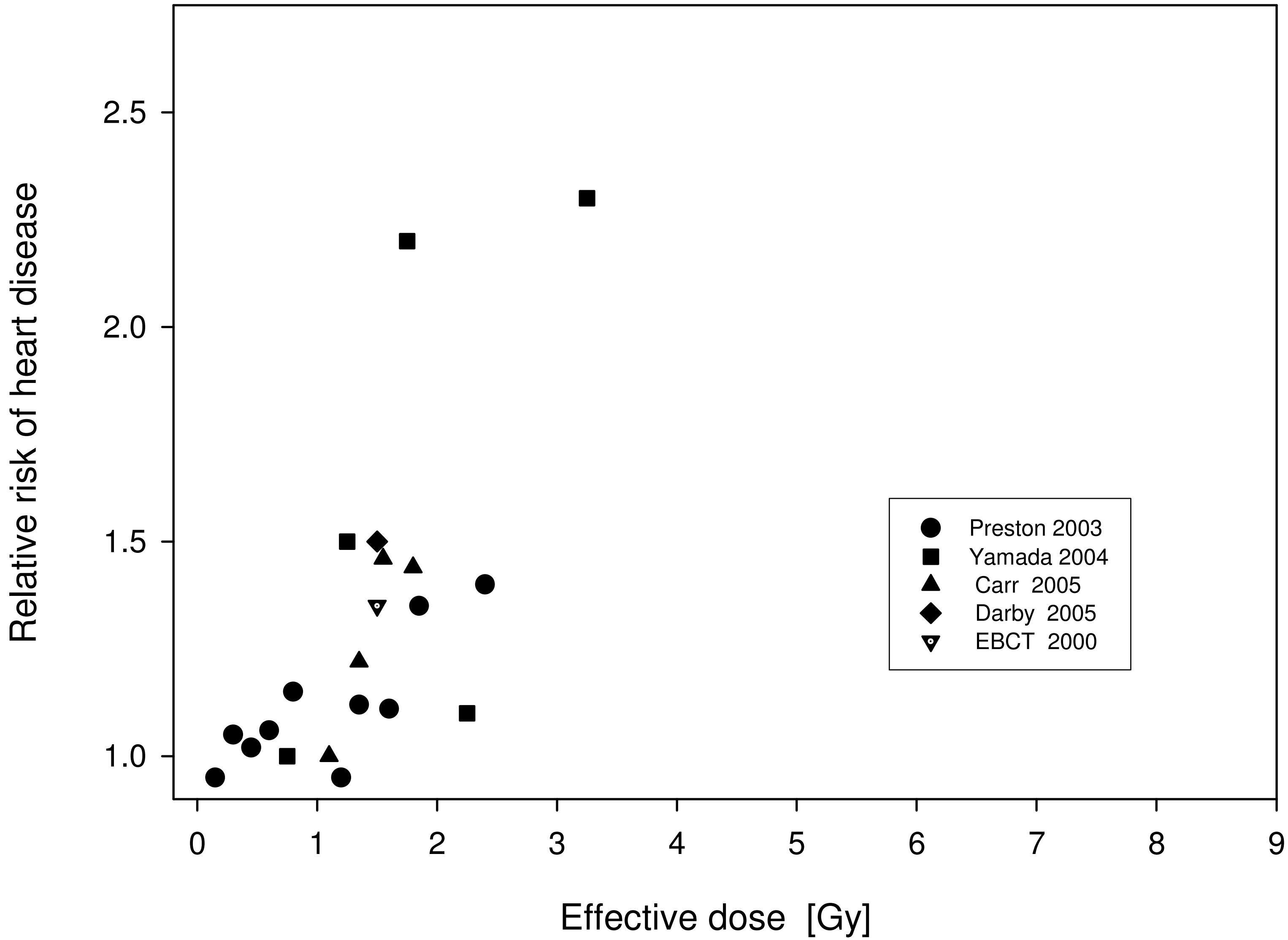
Death rate and absolute difference in annual mortality / 1000

	Years 0-4	Years 5-9	Years 10-14	Years 15-19	Years ≥20
Radiotherapy	53·7	37·6	20·9	15·2	7·2
Control	56·6	44·3	28·6	15·4	5·8
Difference	2·9 (SE 1·6)	6·7 (SE 1·8)	7·8 (SE 1·9)	0·1 (SE 1·9)	-1·4 (SE 1·9)

Deaths / 1000 woman-years and absolute difference in annual mortality / 1000

	Years 0-4	Years 5-9	Years 10-14	Years 15-19	Years ≥20
Radiotherapy	291/38·9	327/22·5	261/11·8	176/6·5	103/2·4
Control	244/34·4	239/18·4	157/9·6	114/5·2	60/2·1
Difference	-0·4 (SE 0·6)	-1·6 (SE 1·2)	-5·7 (SE 1·9)	-5·2 (SE 2·9)	-14·4 (SE 5·5)

Fig. 2 — Absolute effects of radiotherapy on cause-specific survival in the EBCTCG overview [15].



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Effective dose [Gy]
Preston 2003
Yamada 2004
Carr 2005
Darby 2005
EBCT 2000

Hypothesis 1: Radiation increases the frequency of myocardial infarction by interacting with one or more steps of the pathogenic pathway of age related coronary artery atherosclerosis.

Hypothesis 2: Radiation increases the lethality of myocardial infarction, which may occur due to pathologies unrelated to radiation, i.e. by reducing the organ tolerance to minor acute infarctions

as a result of persistent or progressive reduction

of the microcirculation in the irradiated heart.

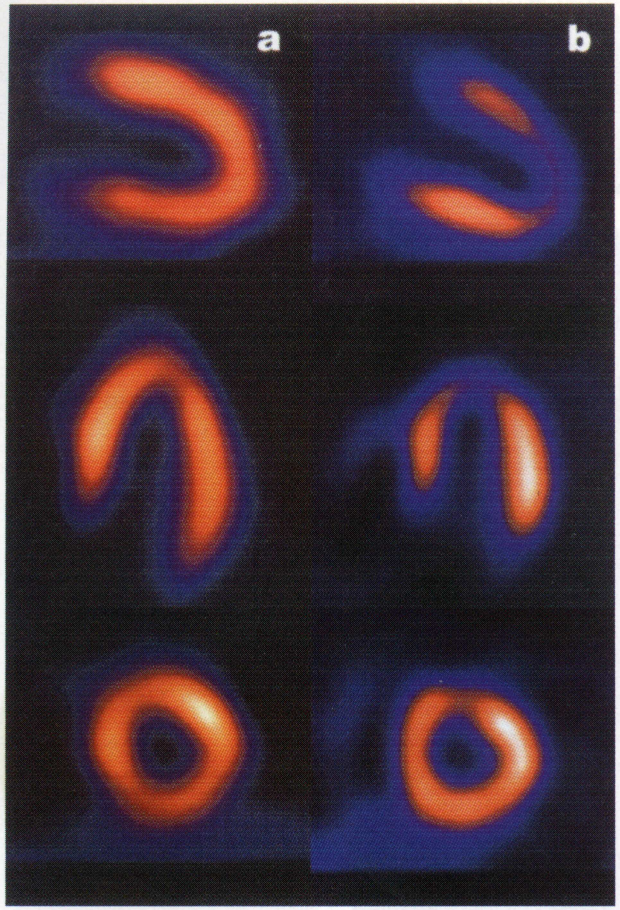


Fig. 3. Horizontal, vertical and short axis views of (a) a normal myocardial perfusion imaging study in a patient treated with right breast radiotherapy, and (b) an abnormal study showing decreased tracer uptake restricted to the cardiac apex in a patient treated with left-breast radiotherapy.

The incidence and functional consequences of radiotherapy associated cardiac perfusion defects

Marks LB et al Int J Radiat Oncol Biol Phys 63: 214-223, 2005

Method:
prospective trial, 114 breast cancer patients enrolled between 1998 and 2001. SPECT cardiac perfusion scans performed before radiotherapy and 6, 12, 18, and 24 months after radiotherapy. The incidence of new perfusion defects related to the dose distribution in the heart.

Conclusion:
“The present study demonstrates that radiotherapy induced cardiac dysfunction is a potentially widespread clinical problem, despite modern radiation techniques.”

Open questions:

Is there a dose threshold of increased risk? Does the latency to clinical manifestation depend on dose as is suggested by experimental data?

What is the clinical nature of cardiovascular disease induced by different radiation doses and dose distributions to the heart?

Is the pathology after low radiation doses different, or the same but developing more slowly, compared to that after high radiation doses?

Which part of the heart is most radiosensitive and should be chosen as a reference point for tolerance doses in radiation oncology or for effective dose to be corrected with an organ weighting factor in radiation protection?

The current European research project RACE aims at solving the following questions:

What is the nature of radiation-induced heart disease after radiotherapy?

Which and where is the critical target in the heart of radiotherapy?

How should the heart dose be specified from treatment plan optimisation?

How does the risk of very late cardiovascular radiation damage depend on the dose to the critical target structures in the heart?

RACE Case-Control Study

Cases: irradiated women who developed heart disease

Controls: irradiated women who did not develop heart disease

-1000+ cases of breast cancer

-Controls matched for: country
age at diag (±1 year)
calendar period (5 years)
RT status

-Individual medical and radiotherapy information

-Detailed dose estimation

-Sweden, Denmark

-Objective: Dose response relationship for use in evaluating risks from current and planned treatments

-Funding: EC 6th Framework, CTSU, other

Case-case study

Population:

Denmark

Sweden

Cases = women irradiated for breast cancer who develop coronary heart disease prior to any recurrence of their breast cancer.

Aims:

- Association between type of coronary heart disease and radiation dose?
- Association between the spatial damage to the heart and anatomical distribution of radiation dose?
- Which cardiac structures are the most sensitive to radiation dose?

The European Research project CARDIORISK aims at solving the following problems:

Is very late cardiovascular radiation damage caused by radiation damage to the coronary arteries or to the microvasculature?

Which radiation-induced changes in endothelial cell function is responsible for very late cardiovascular radiation damage?

What is the role of inflammation and of the immune response in the pathogenesis of very late cardiovascular radiation damage?

Can progressive very late cardiovascular radiation damage be mitigated by early post-radiotherapy pharmacological intervention?

Methods used in CARDIORISK:

Functional imaging of the microvasculature of the heart and the vascular patency of the irradiated arteries

Histopathological investigations. The main criterion in the hearts will be the microvascular density and evidence for focal hypoxia in relation to the changes observed by functional imaging.

Ex vivo investigations of the irradiated arteries.

In vitro investigations. Endothelial cells will be isolated from irradiated hearts and, in the pilot experiments from repair blastemas, at different times after local irradiation.

Proteomics

Open questions

- Where is the critical structure where the dose in the heart has to be calculated?
- Does cardiovascular risk increase with dose after a threshold dose or without?
- Does the latency depend on dose?
- Does the risk depend on age at exposure?
- Which cardiovascular disease is caused by low and medium radiation doses?

The end

Summary: Aims of CTSU research program

•Examine cardiac incidence and mortality left-sided vs right-sided in women irradiated for breast cancer

•Derive dose-response relationships for radiation-induced heart disease

•Study the relationship between location of cardiac damage and spatial distribution of radiation dose to the heart

Radiation Associated Cardiac Events (RACE)

Objectives:

- Derive dose-response relationships for radiation-induced heart disease
- Study the relationship between location of cardiac damage and spatial distribution of radiation dose to the heart

Collaborators:

- CTSU: Sarah Darby, Paul McGale, Richard Peto, Kazem Rahimi, Carolyn Taylor
- Royal Surrey County Hospital: Andy Nisbet
- Karolinska Institute: Per Hall, Anna Bennet, Giovanna Gagliardi, Bruna Gigante, Ulla Goldman
- University of Aarhus: Marianne Ewertz
- Danish Breast Cancer Collaborative Group: Maj-Britt Jensen

Ongoing and planned research on radiation-induced heart disease in radiotherapy

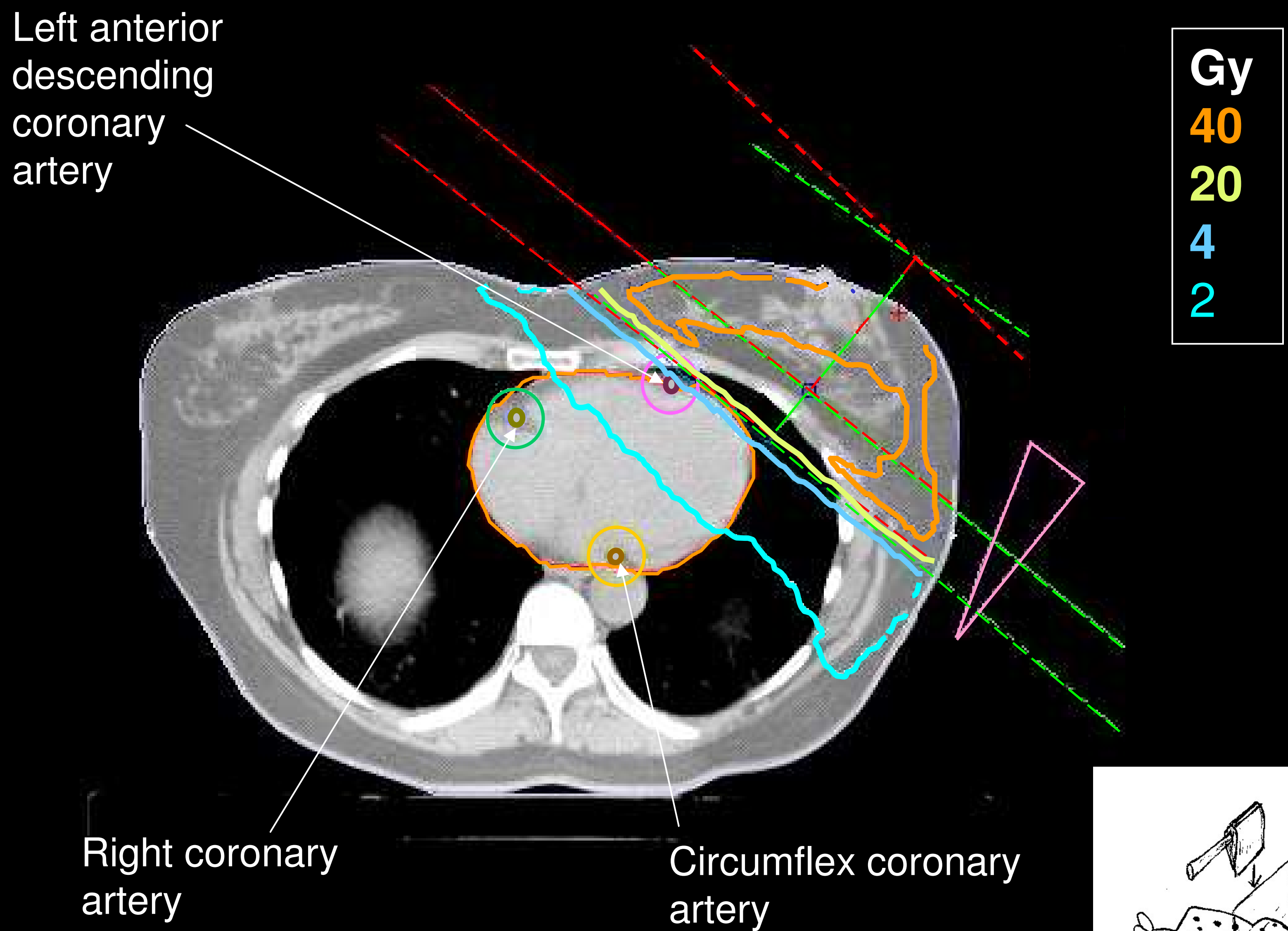
Measurement of microvascular perfusion changes and their relation to anatomical radiation dose distribution in the heart

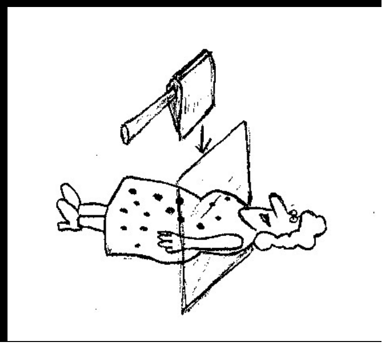
Case control studies on the relation of cardiovascular disease to radiation dose distribution (RACE)

Cardiovascular risk after occupational exposure **?**

Cohorts investigated:	result	author
Uranium miners	-	Kreuzer, 2006
Chernobyl liquidators	+?	Ivanov, 2006
Sellafield nuclear workers	+	McGeoghegan
Mayak nuclear workers	+	Muirhead 2008

Left breast irradiation





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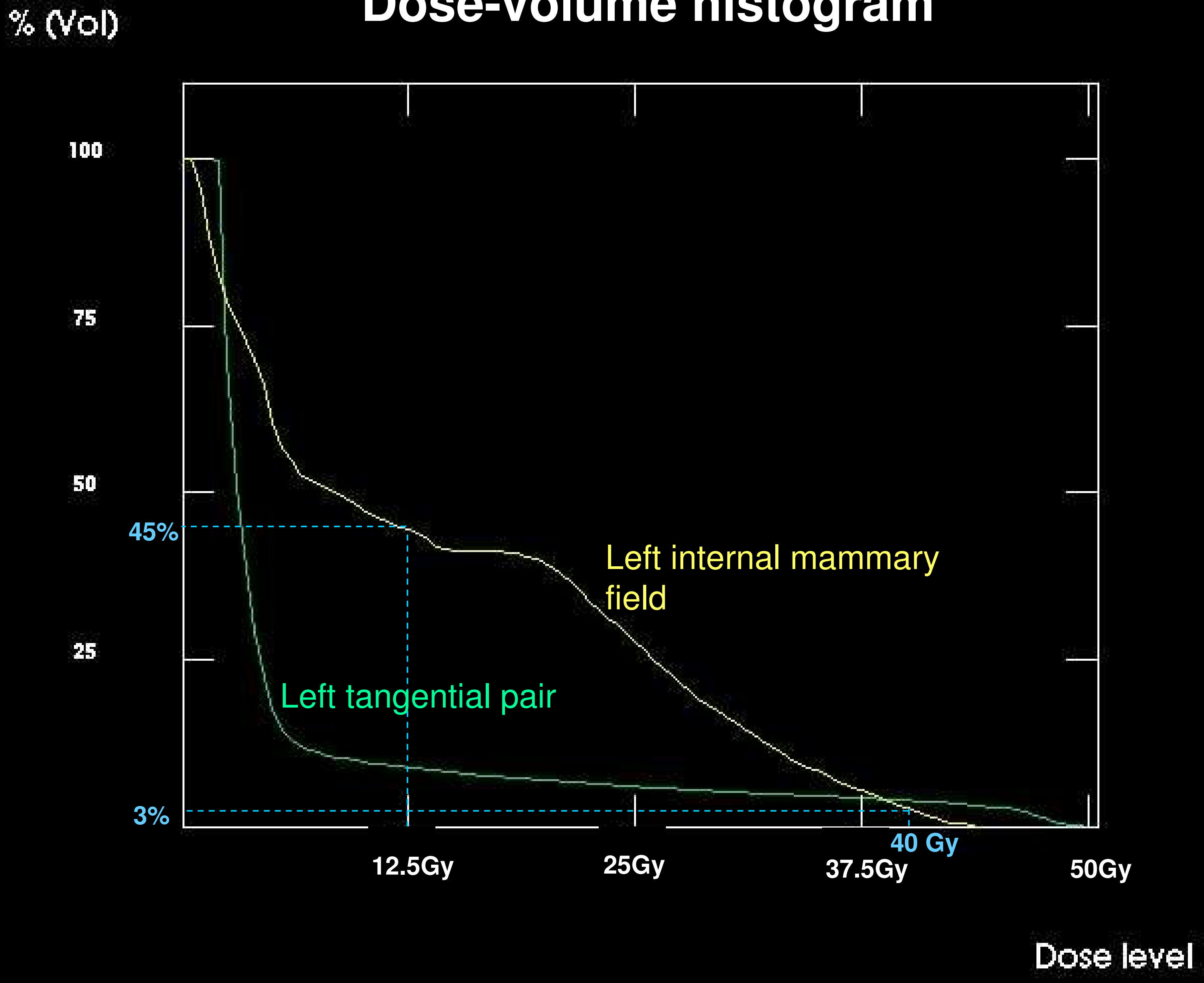
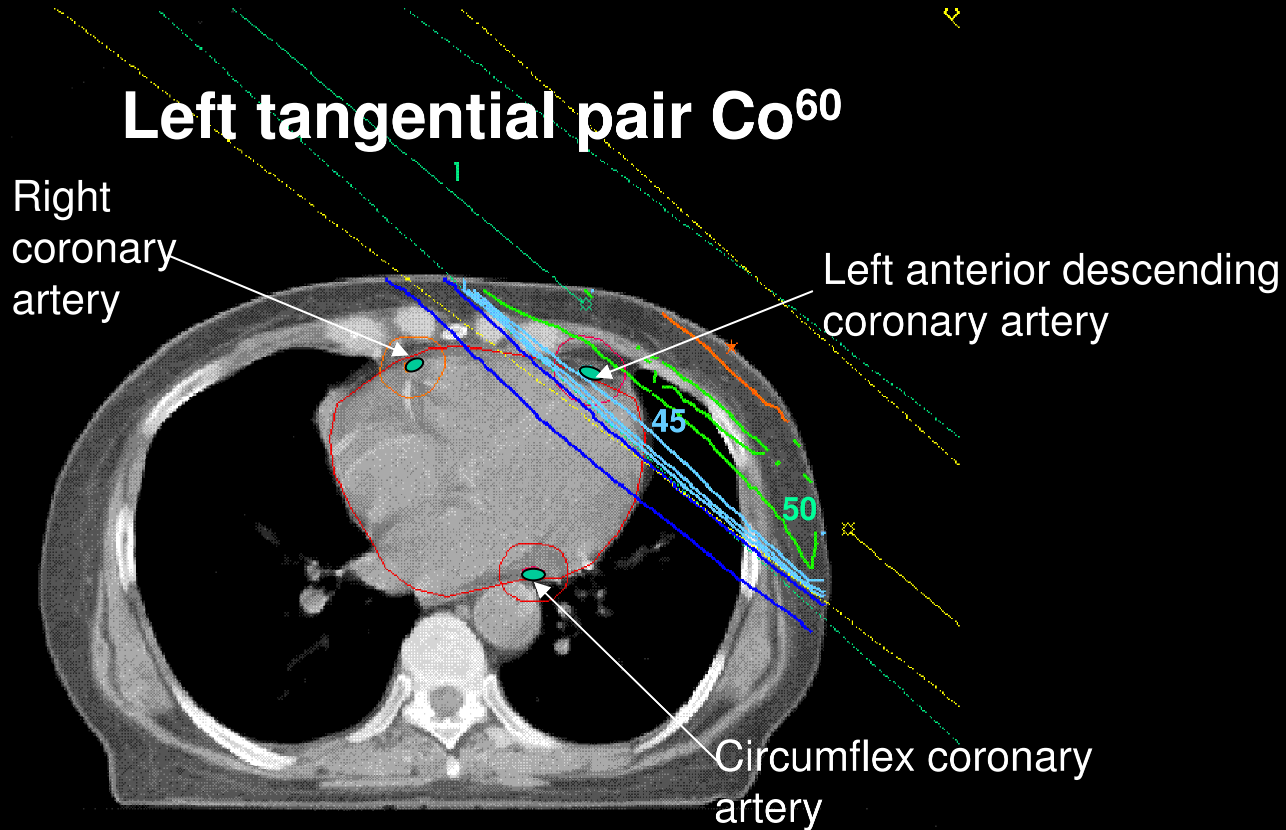
Estimation of cardiac doses: RACE

Dose-volume histogram



Left tangential pair Co^{60}



Target	Field arrangement	Beam energy	Typical dose	Mean dose (Gy)			
				Heart	LAD	RCA	Circ
Left chest wall/ breast	Tangential pair	6MV	50 Gy in 25	5	22	2	3
		Co-60	50 Gy in 25	5	22	2	3
		250 kv	42 Gy in 20	14	51	11	8

Taylor et al. Int J Radiat Oncol Biol Phys (2007)