Cardiovascular disease after radiation therapy

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Radiation induced long-term health effects after medical exposure

The principles of Radiation Therapy

- The ideal radiation source: the ”infinitron” - 100% of the energy delivered to the tumour, zero energy outside

- Brachytherapy comes close (source of short-range radiation inside the tumour).

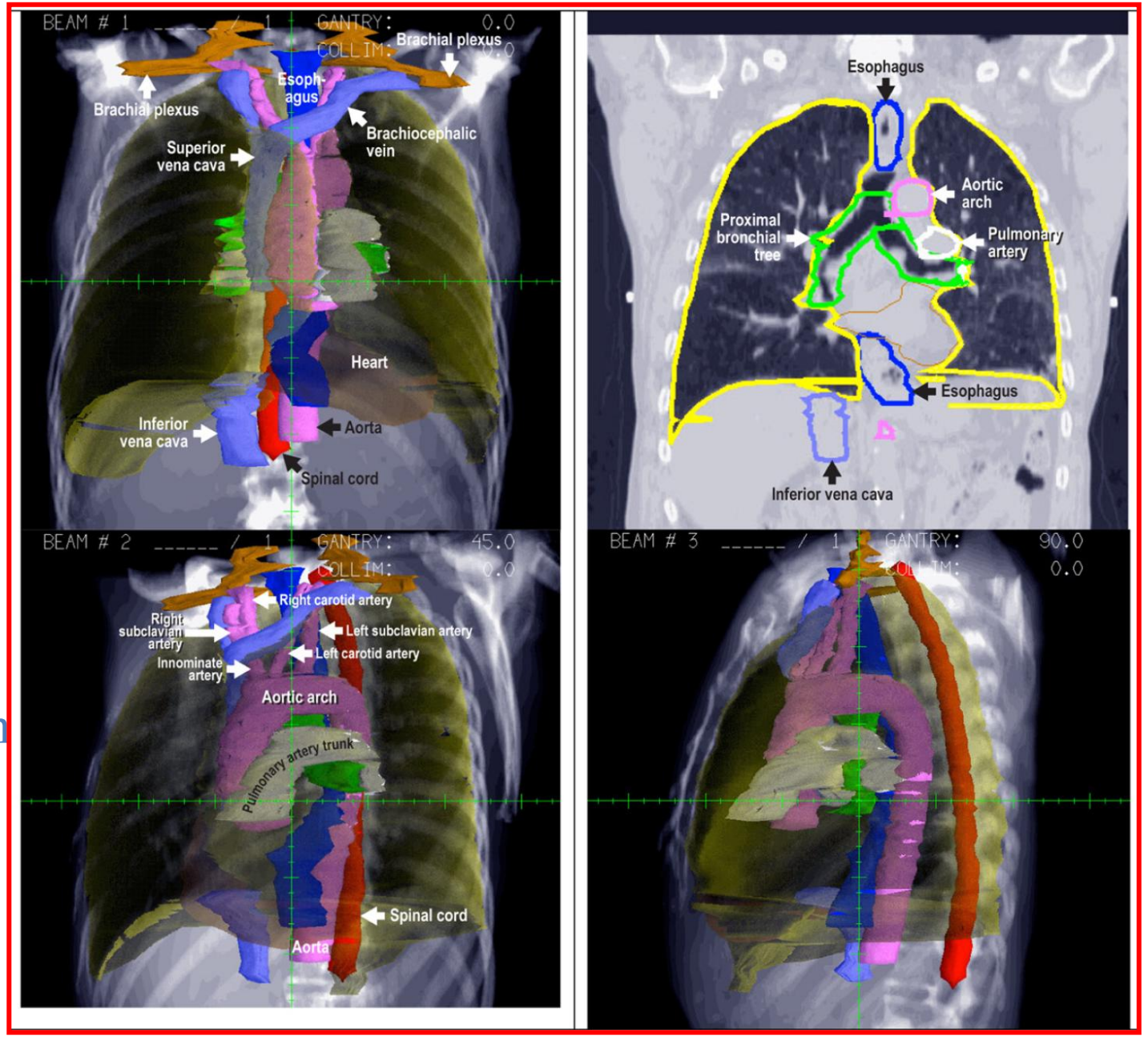
- Real (external) beams deliver energy from the patient skin all the way to the tumour and beyond and also laterally (due to scatter). Therefore irradiation of non-tumour tissue is unavoidable.

- The aim of radiotherapy treatment planning is to find the best compromise between tumour elimination (= ’control’) and complication avoidance.

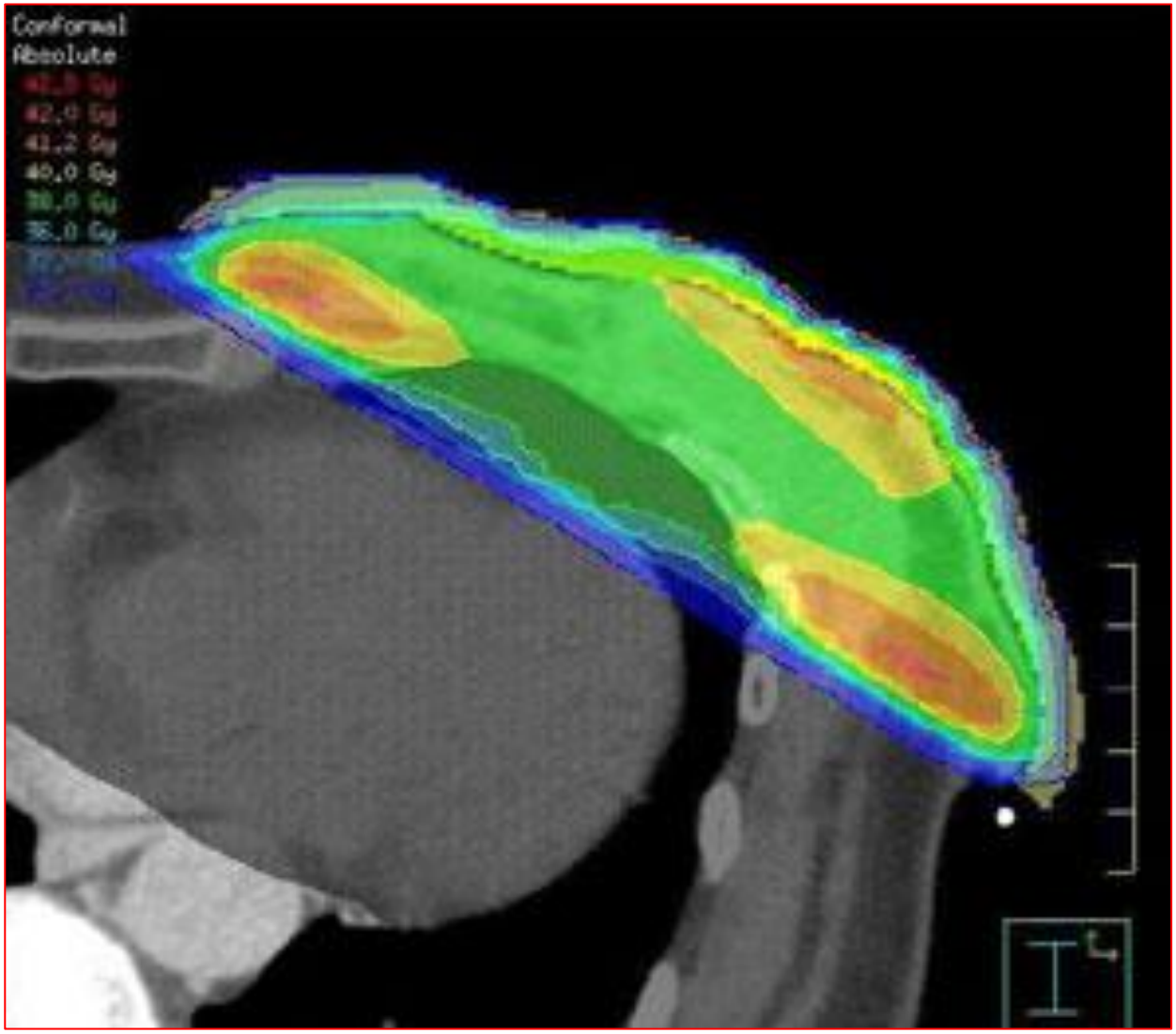
When irradiating the thorax:

From Kong *et al*, 2010

- **Heart**
- Lung
- Esophagus
- Ribs
- Chest wall pain
- Liver



Dose distribution **(example)**

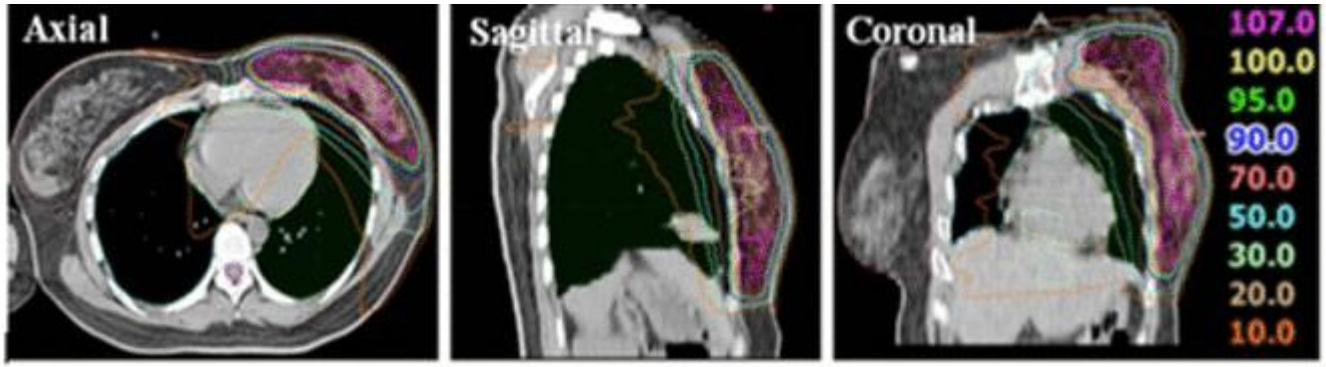


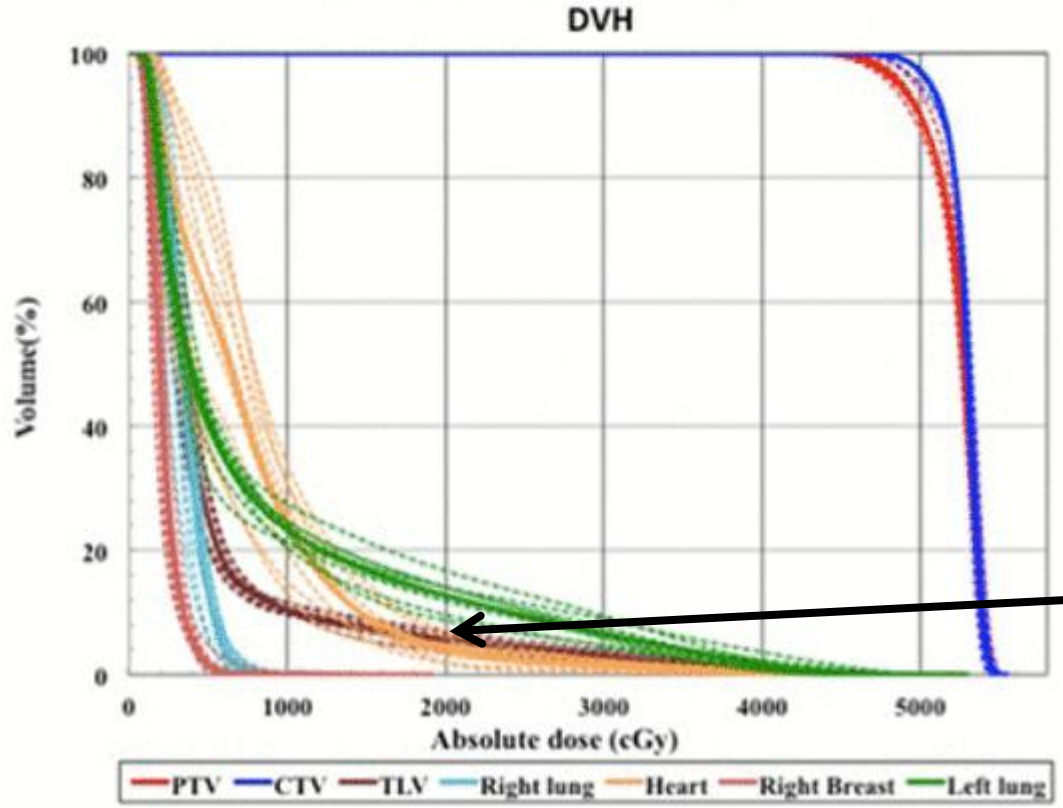
Breast ca, left lung, heart

Typical treatment prescription:

46 Gy,
2 Gy/fr

Tool to summarize 3D information in a 2D picture





Dose-Volume Histograms (DVH)

Each point represents the percentage of the volume of the structure receiving at least that dose

V20

Radiation induced heart disease

- Spectrum of clinical syndromes:

  pericardial disease, myocardial disease, valvular defects, coronary artery disease
- Clinical data come from population of radiotherapy patients - breast cancer, lymphoma, seminoma, lung cancer
- Studies from the 1960s demonstrated the radiosensitivity of the heart and of the vascular structure
- Not many dose-volume response relationships have been quantified

Reference	Diagnosis, # patients, years of treatment	OAR	Fractionation schedule Dose data	Predictive parameters ⇧	NTCP parameters ⇧
*Carmel and Kaplan 1976	Hodgkin's 377 pts 1964-1972	Pericardium		$D_{pericardium}$ >30 Gy 50% pericarditis, 36% requiring treatment	
Cosset *et al* 1991	Hodgkin's 499 pts 1971-1984		35-43 Gy/ 2.5-3.3 Gy/fr pre-3D dose data	$D_{Mediastinum} \geq 41$ Gy d/ fraction ≥ 3 Gy (marginal significance)	
Burman *et al* 1991	Historical data				LKB *TD50*=48 Gy *m*=0.10 *n*=0.35
Martel *et al* 1998	Esophagus 57 pts 1985-1991	Pericardium	37.5-49 Gy/ 1.5-3.5 Gy / fr 3D data	D_{mean}>27.1 Gy D_{max}> 47 Gy d/ fraction 3.5 Gy	LKB (*CI 95%*) *TD50*=50.6 Gy (-9; 23.1) *m*=0.13 (-0.07; 0.13) *n*=0.64 (-0.58; 3)
Wei *et al* 2008	Esophagus 101 pts 2000-2003	Pericardium	45-50.4 Gy 1.8-2.0 Gy/fr 3D data	D_{mean}pericardium > 26.1 Gy V_{30} < 46%	

Pericarditis, **Gagliardi *et al*, 2010**

Pericarditis - acute effect

- 101 pts,esophagus ca, (2000-03),
  27% crude incidence
  pericardium DVH better than heart DVH
  V_{30} < 46%, MD < 26 Gy

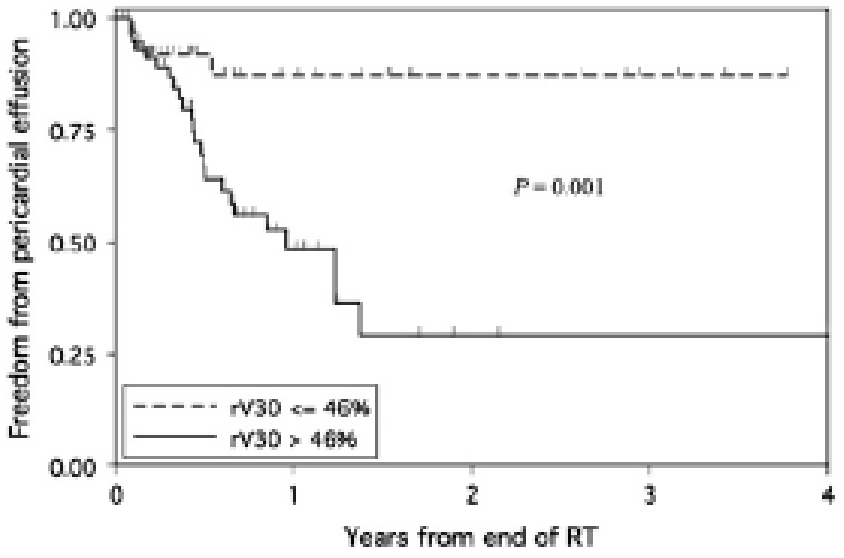
(Wei X et al, IJROBP 2008)

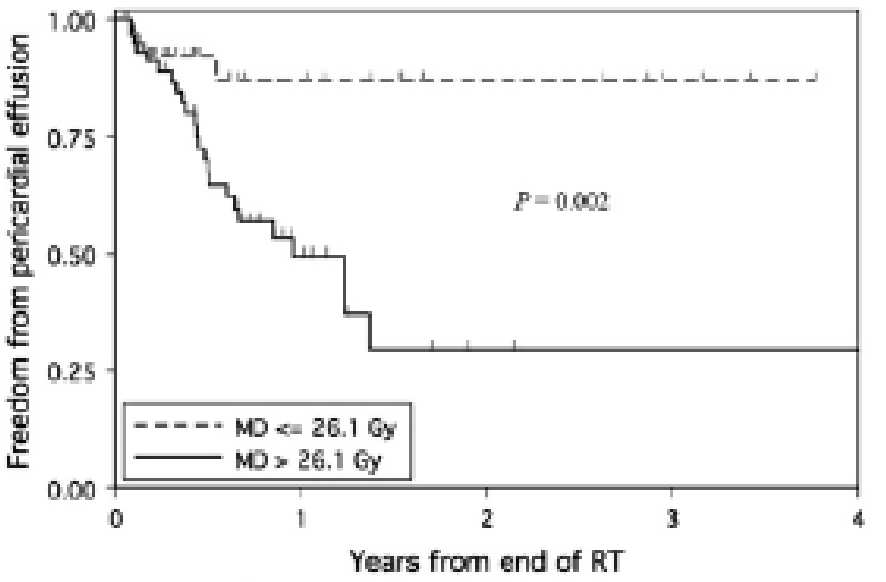
- 377 Hodgkin's pts (1964-72),
  D_{mean} pericardium >30 Gy
  50% pericarditis, 36% requiring treatment

(Carmel Kaplan 1976)

- 140 Hodgkin's pts (1964-81)
  D mediastinum ≥ 41 Gy

(Cosset 1991)



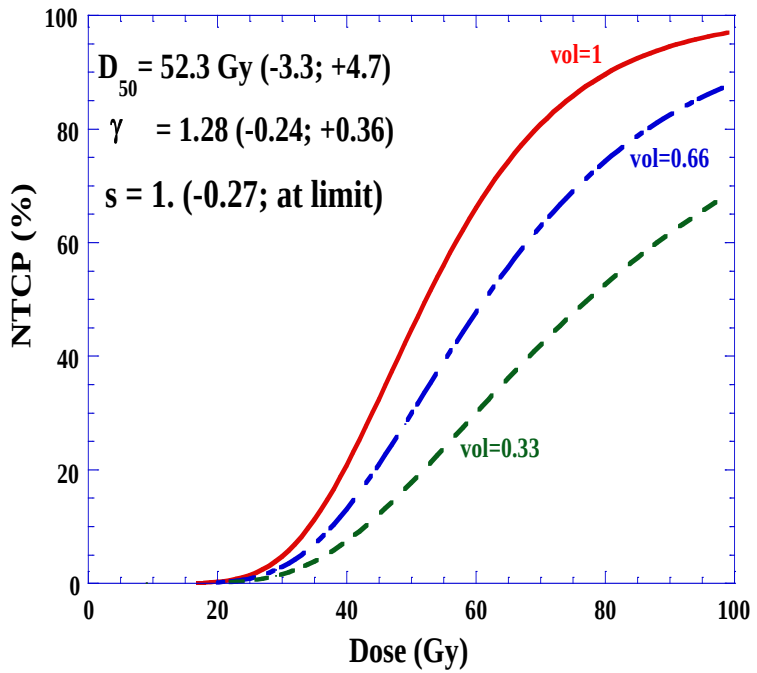


Heart: Long-term cardiac mortality

Gagliardi *et al*, 2010

Reference	Diagnosis. # patients, years of treatment	OAR	Dose data	Predictive parameters	NTCP parameters
Hancock *et al*. 1993	Hodgkin's 2232 pts 1960-1990	heart	dose up to 44 Gy pre-3D dose data	$D_{mediastinum}$ > 30 Gy	
Gagliardi *et al* 1996	Breast 809 pts 1964-1976	heart*	45-50 Gy1.8-2.5 Gy/fr treatments reconstructed in 3D on average patients		RS *(CI 68%)* *D50*=52.3 Gy (49;57) γ=1.28 (1.04;1.64) *s* =1 *(0.63;at limit)*
Eriksson *et al* 2000***	Hodgkin's 157 pts 1972-1985	heart	≈ 40 Gy 2 Gy/fr individual treatments reconstructed in 3D on phantom	D_{35} > 38 Gy	RS: Hodgkin's *D50*=70.3 Gy γ=0.96 *s* =1 *RS: Hodgkin's + breast* *D50*=63 Gy γ=0.94 *s* =1
Carr *et al* 2005	Peptic ulcer 1859 pts 1936-65	heart (Alderson Phantom)	1.5 Gy /fr 250-kVp X-rays treatment simulated on phantom	D_{mean} to 5% >12 Gy heart volume within the beam D_{mean}>2.5 Gy whole heart volume	
Paszat *et al* 2007	Breast 619 pts 1982-1988	heart	40-50 Gy 2-2.67 Gy/fr pre-3D dose data	RT to IMC	

Long-term cardiac mortality



- Breast cancer data (Oslo and Stockholm randomized trials)
- NTCP - RS model, 3D reconstruction of treatment techniques
- weak volume effect
- heart definition, comparison with myocardium DVH

Gagliardi et al, Br J Rad. 1996

- Normal Tissue Complication Probability Modelling (NTCP)
- The data behind the modelling: →

CLINICAL DATA (NTCP)

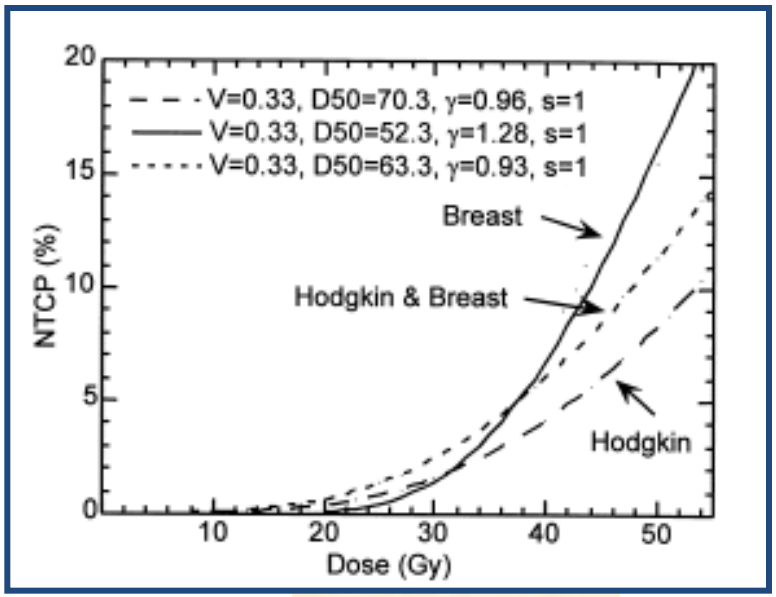
- Oslo breast cancer trial: 1968-72
- endpoint: death from myocardial infarction (FU > 11 ys)
- ant. field to the sternal nodes, ^{60}Co; 50 Gy, 2.5 Gy/f

excess cardiac mortality: **7.9% ± 3.7% (left);**
3.3 % ± 2.7 % (right)

- Stockholm breast cancer trial: 1971-76
- endpoint: death from ischemic heart disease (FU > 13 ys)
- tang.fields to the chest wall and IMC ^{60}Co; 45 Gy, 1.8 Gy/f

excess cardiac mortality: **6.8% ± 3.5% (left)**
0% (right)

- oblique e-field: **0% (left)**



Hodgkin's data and breast data:

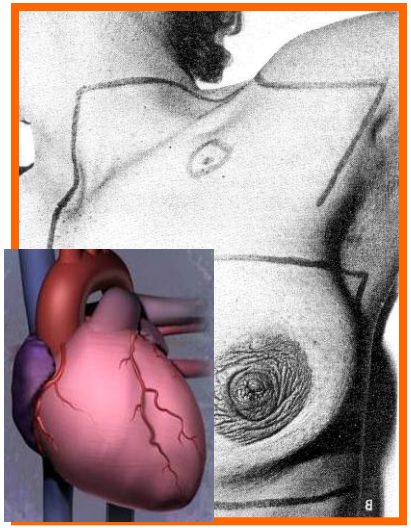
1) different parts of heart irradiated (almost complementary)

2) breast dose-response curve: steeper-safer (think of LDA location in tangential fields irradiation)

Eriksson F, *et al. Radiother Oncol* 2000;55:153–162.

Cardiac mortality modeling problems:

- Clinical data: low number of events (registers are needed)
- Long-term complications
- Dosimetrical data (retrospective studies; lack of 3D information)



by courtesy of C.Taylor,Oxford

The NEW ENGLAND JOURNAL of MEDICINE

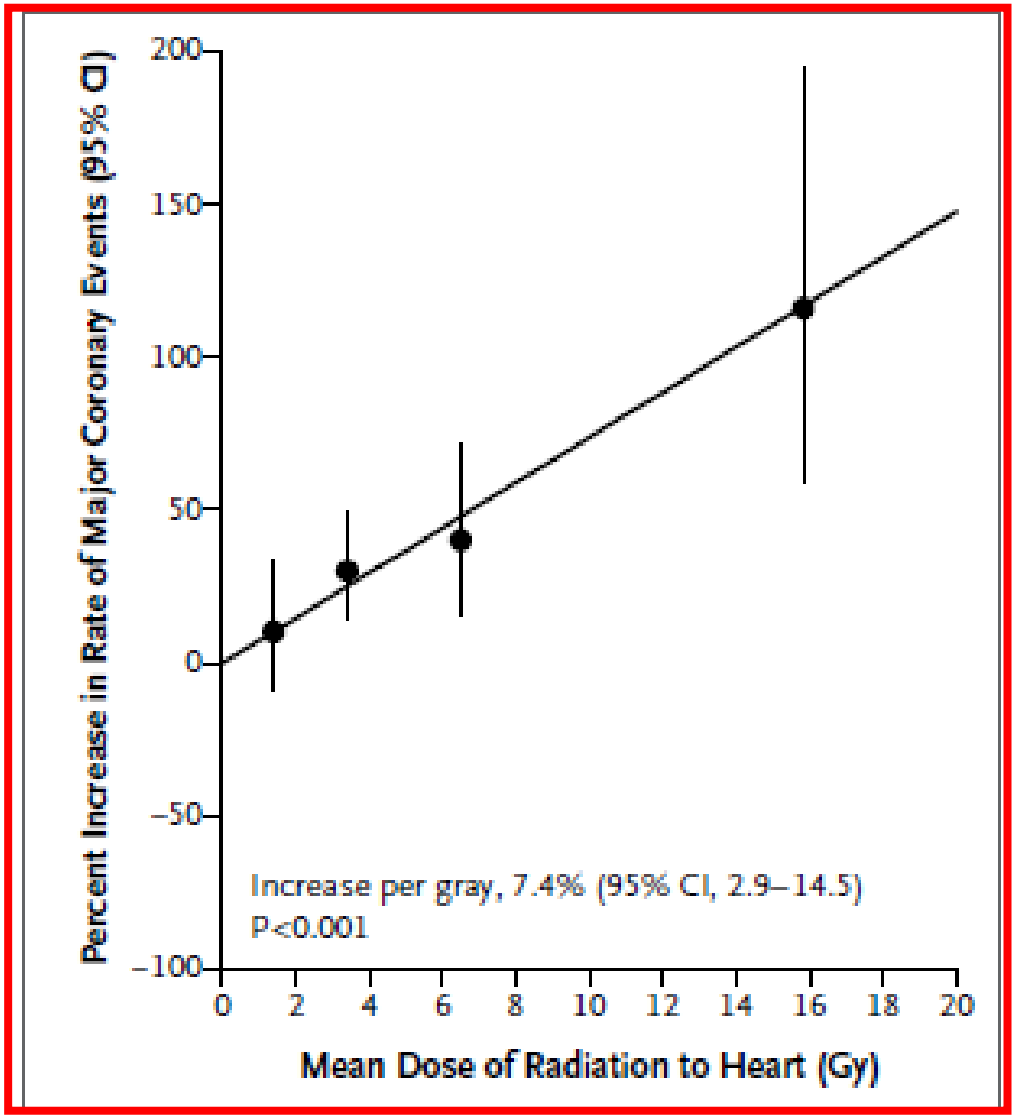
ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

- Population based case-control study of major coronary events (i.e. myocardial infarction, coronary revascularization, death from ischemic heart disease)
- 2168 breast ca pts, RT (963 cases, 1205 controls) treated between 1958 and 2001
- Mean dose to the whole heart and to left descendent artery (from hospital charts)

- Mean dose to heart = 4.9 Gy (range:0.03-27.72)
  left sided: 6.6 Gy, right sided: 2.9 Gy
- Rates of major coronary events increase linearly with mean dose to heart by 7.4% per Gray, no threshold (compared to the non irradiated population)
- Debut within the first 5 yrs after RT, continuing into the third decade after RT
- Women with pre-existing cardiac risk factors: greater absolute increase in risk, than other women

Darby S *et al*, N Engl J Med 2013



Major coronary events:

- -Myocardial infarction
- -Coronary revascularization
- -Death from ischemic heart disease

Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Major coronary events included myocardial infarction, coronary revascularization, and death from ischemic heart disease. The values for the solid line were calculated with the use of dose estimates for individual women.

- compared to non irradiated women
- not corrected for fractionation (but this does not change the picture)

Darby *et al*, 2013

Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer

K E Henson*[,1], P McGale[1], C Taylor[1] and S C Darby[1]

Mortality ratios, by laterality of breast ca, were estimated for >500.000 women recorded with breast ca during 1973-2008 in the Surveillance, Epidemiology and End Results (SEER) cancer registries and followed until jan 2009.

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- For women diagnosed with breast ca and treated with RT, the cardiac mortality ratios, left-sided vs right-sided

	<10years	10-14 ys	15-19ys	20+
1973-1982	1.19	1.35	1.64	1.90
1983-1992	0.99	1.02	1.11	1.21
1993-	0.97	0.9		-

- For women receiving RT after 1982, almost no evidence of any radiation related increase in heart disease mortality compared to earlier treatments

- Points to note - new treatment guidelines? too short follow-up? Quality of dose-volume data (**no individual radiation dose available**)

- Decline in the use of internal mammary nodes

  → Change of target and treatment techniques, not of dose prescriptions

Henson KE *et al*, BJC2013

- Left breast ca pts, with internal mammary chain
  mean heart dose: 13-17 Gy - ”earlier”

- Left breast ca pts, (decreased irradiation of IMC)
  mean heart dose: 2-7Gy - ”currently”

→ ***risks for women irradiated today are likely to be lower***

Henson KE *et al*, BJC2013, Taylor *et al*, 2008

Example from the clinic:

Current treatments	Mean dose (Gy)
stage I (50 pts)	**2.8 Gy (0.0-8.2)**
stageII (50 pts)	**3.4 Gy (1.3, 6.4)**

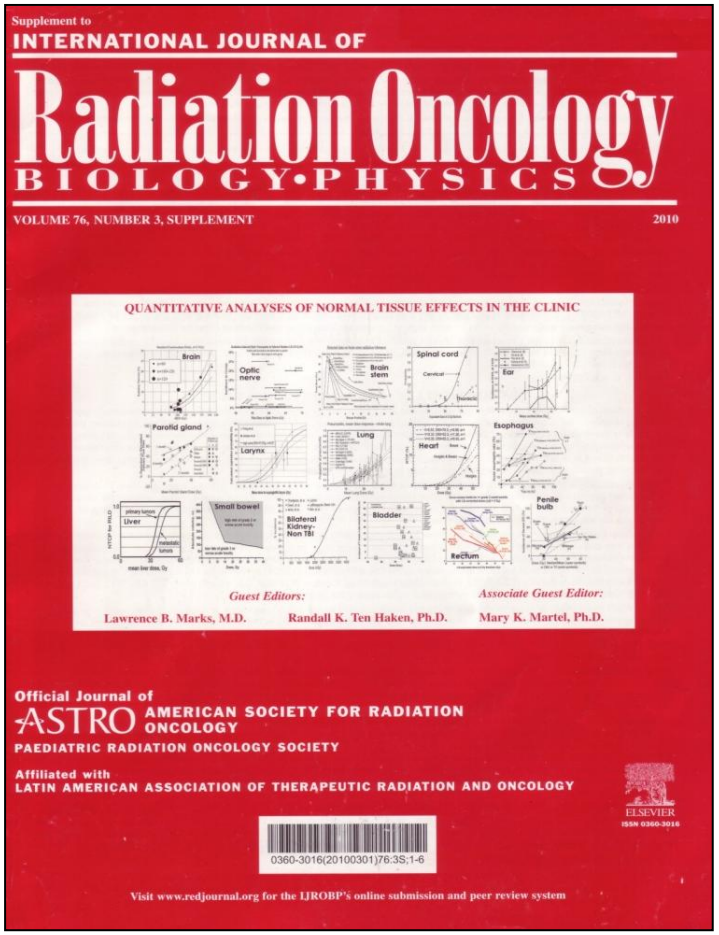
QUANTEC, 2010 ASTRO-AAPM

Quantitative Estimates of Normal Tissue Effects in Clinic

Summary of the knowledge

- Each constraint is associated with the incidence of a particular complication or toxicity.
- The choice of the constraint is a choice of the toxicity rate.

This choice is left to the responsibility of the user.



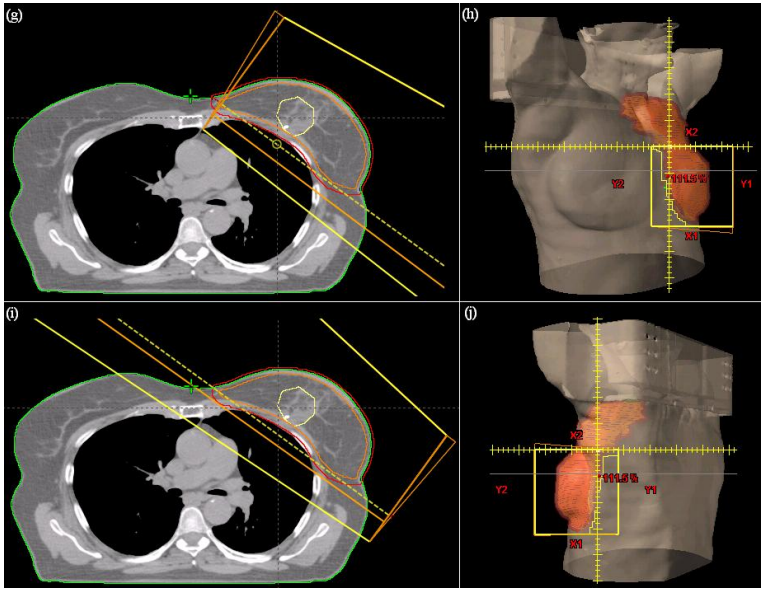
QUANTEC group was formed from a loose network of researchers with a longstanding interest in dose–volume modeling. The Steering Committee defined three aims for QUANTEC.

(1) To provide a *critical overview of the current state of knowledge* on quantitative dose–response and dose–volume relationships for clinically relevant normal-tissue endpoints
(2) To produce *practical guidance* allowing the clinician to reasonably (though not necessarily precisely) categorize toxicity risk based on dose–volume parameters or model results
(3) To identify *future research avenues* that would help improve risk estimation or mitigation of early and late side effects of radiation therapy

Cardiovascular disease following radiation therapy

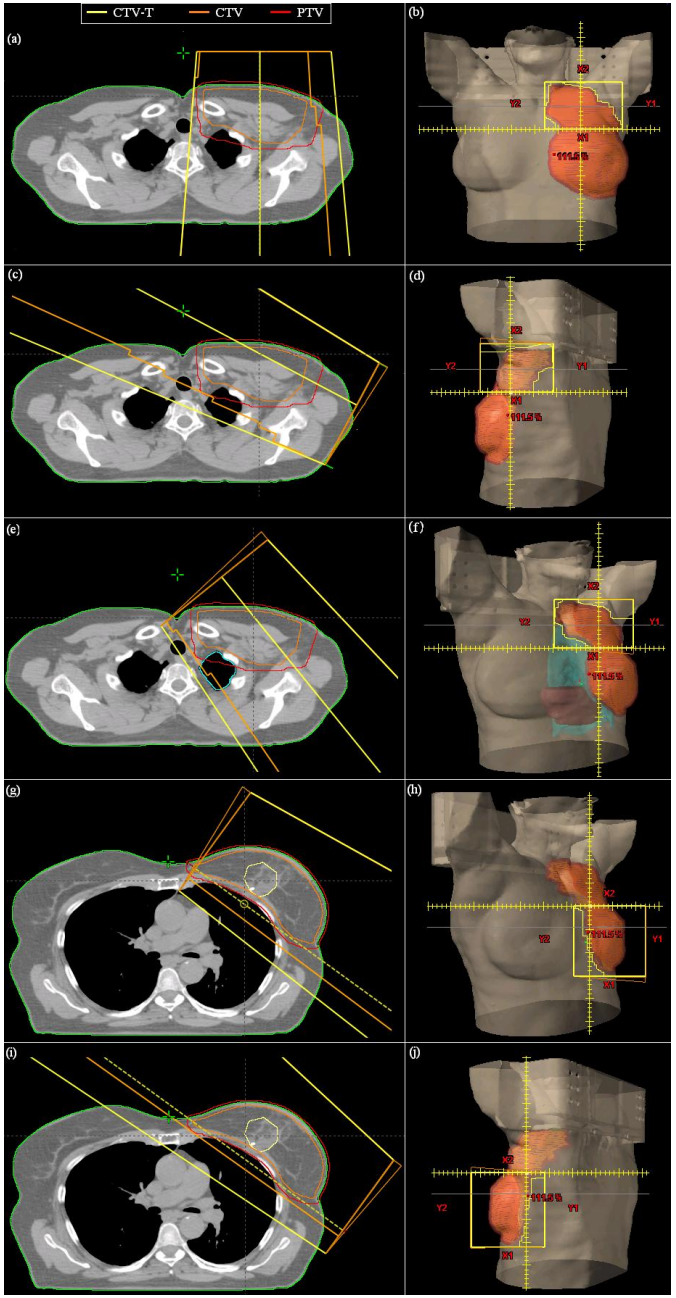
Pericarditis	**Mean Dose < 26 Gy V30<46%**
Long-term cardiac mortality	**V25<10%**

QUANTEC summary of data, 2010



Example from the clinic - Breast-stage I

	V25 (%)	NTCP (%)	Mean dose (Gy)
Average	2,9	0,3	2,8
Std	1,9	0,2	1,2
Min	0,0	0,0	0,7
Max	8,2	0,9	6,6



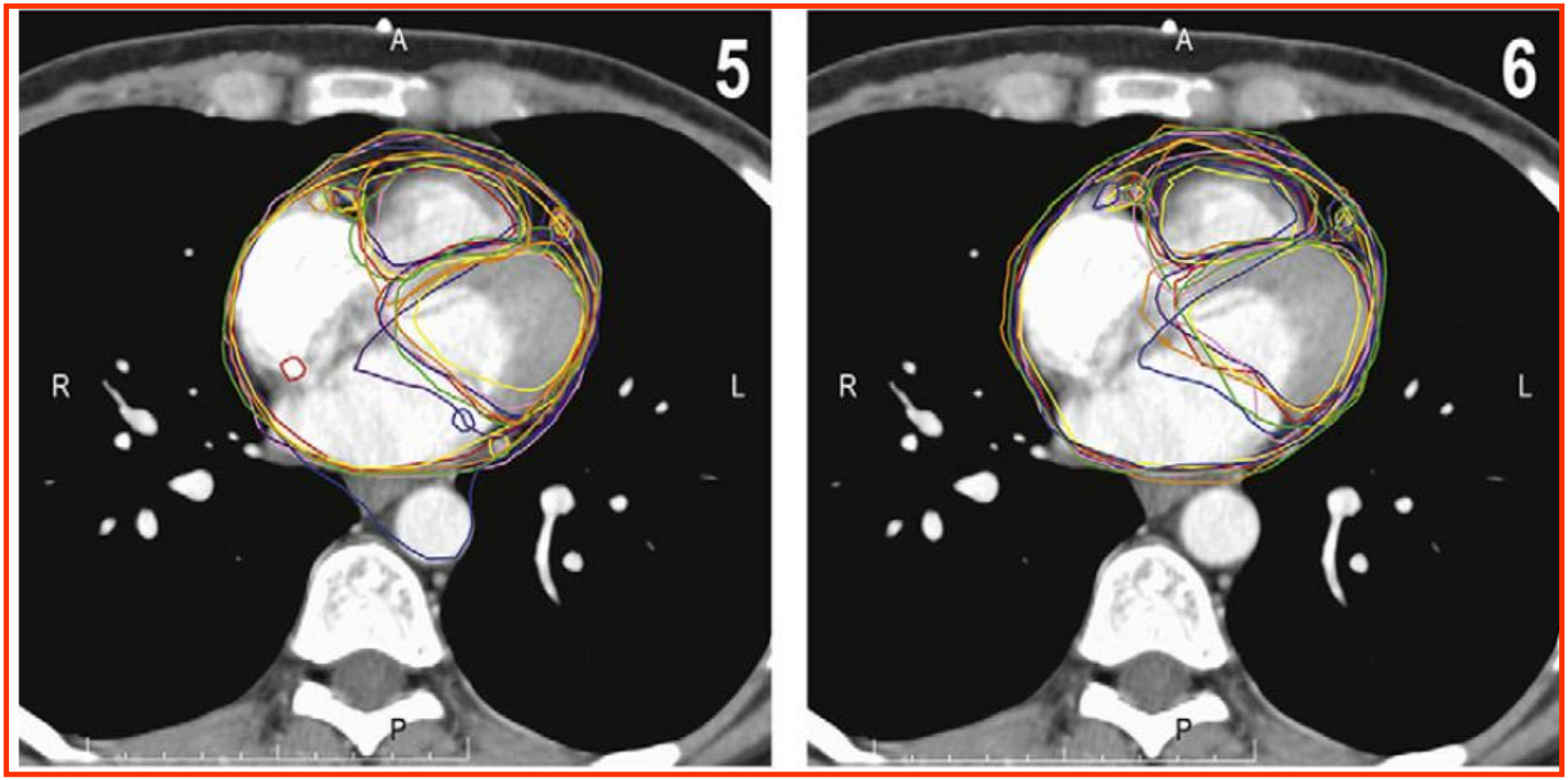
Example from the clinic - Breast-stage II

	V25 (%)	NTCP (%)	Mean dose (Gy)
Average	3,2	0,3	3,4
SD	2,2	0,3	1,3
Min	0,0	0,0	1,3
Max	7,9	0,9	6,4

Cardiovascular disease following radiation therapy

Still open issues

- Quantification of dose-volume response for relevant substructures, e.g. left descendent artery/delineation
- More specific dose-volume predictors?
- **How to identify women at risk?**
- ….What to say and how to say it?



From Feng *et al*, 2011

Delineation of subvolumes within the heart

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