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Bologna

Radioterapia nel trattamento del carcinoma mammario e cardiotossicità:

un problema reale, da quantificare, da evitare

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Radioterapia nel trattamento del carcinoma mammario e cardiotossicità

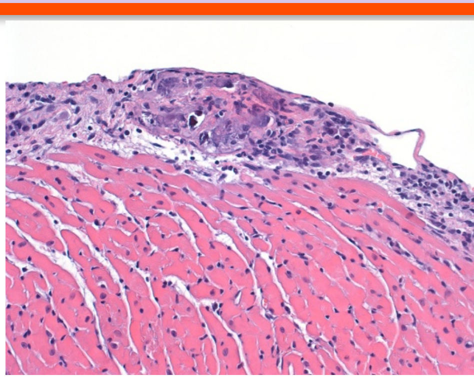
Un problema reale

Da quantificare

Da evitare

Cardiovascular Complications of Radiotherapy

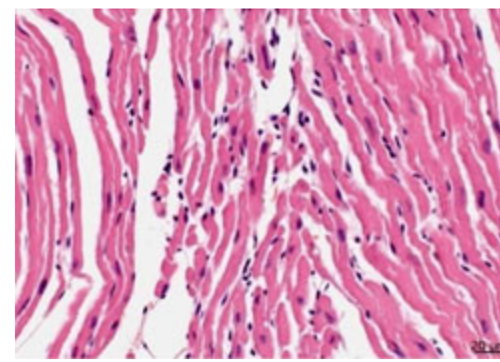
Pericardial Disease



Acute pericarditis: immediately after radiotherapy to 2 years later

Minority develop ***chronic pericarditis*** with effusion or pericardial constriction

Physiopathology: Increased vascular permeability, fluid extravasation, inflammatory cell infiltration.
Fibrous thickening, fibrinous pericardial adhesions



Cardiomyopathy

Increase TGF-β, FGF-2 → ***fibroblast activity*** and ***proliferation***

Damages intercalated discs and inhibits cardiac mitochondrial respiration → elevated ***production of ROS*** and ***myocardial dysfunction***

Activation renin-angiotensin-aldosterone system → increase angiotensin II → Increase TGF-β and ***fibroblast activity***

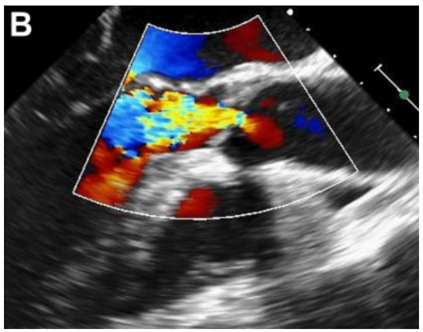
Lee, M. S. (2013) *Am J Cardiol* **112**(10): 1688-1696. Stewart, F. A., (2013) *Clin Oncol* **25**(10): 617-624.

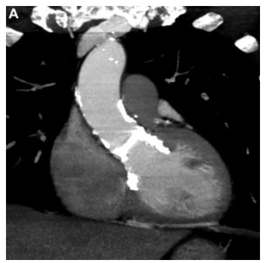
Cardiovascular Complications of Radiotherapy

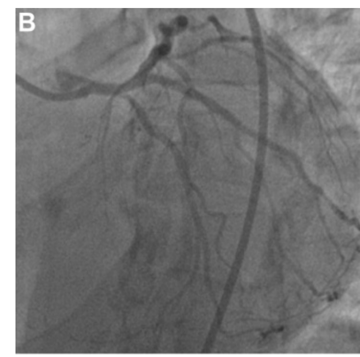
Valvulopathy

Valve thickening, calcification → stenosis, regurgitation

Increase expression of alkaline phosphatase, bone morphogenetic protein 2 and osteopontin → Aortic valve interstitial cells convert to osteoblastlike cells







Coronary Artery Disease

Angina (more common), ***acute coronary syndrome, heart failure***

Activation of intima and media lysosomal enzymes → atherosclerosis
Endothelial injury → ROS
Release of von Willebrand factor and decreasing the production of thrombomodulin → increases the adhesiveness of endothelial cells

Lee, M. S. (2013) *Am J Cardiol* **112**(10): 1688-1696. Stewart, F. A., (2013) *Clin Oncol* **25**(10): 617-624.

Radioterapia nel trattamento del carcinoma mammario e cardiotossicità

Un problema reale (??)

Clinical outcome

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

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

Darby, S. C., (2013) *NEJM* **368**(11): 987-998

Clinical outcome

The NEW ENGLAND JOURNAL of MEDICINE

Population-based ***case–control study***

Breast cancer (Swedish National Cancer Register and Danish Breast Cancer Cooperative Group), younger than 70 years at diagnosis, years:1958-2001.

- ***Case: Major coronary events***: myocardial infarction, coronary revascularization, death from ischemic heart disease. Angina alone were not included
- ***Control: Patients without major coronary events*** (random selected, one per case patient in Sweden and two per case patient in Denmark)

Radiation Dosimetry: CT planning on the CT scan of a woman with typical anatomy; DVH for the whole heart and for the left anterior descending coronary artery

Darby, S. C., (2013) *NEJM* **368**(11): 987-998

Clinical outcome

Tumor characteristic

Characteristic	No. of Case Patients (N=963)	No. of Controls (N=1205)	Rate Ratio	P Value†
Tumor characteristics				
Nodal status				0.06
Negative	482	610	1.00	
Positive	463	579	1.20	
Unknown	18	16	0.96	
Size				0.97
<2 cm	331	449	1.00	
2–5 cm	494	604	1.00	
Other or unknown	138	152	1.08	
Location				0.22
Outer quadrants	350	572	1.00	
Inner quadrants	114	204	0.84	
Other or unknown	499	429	0.82	
Laterality of breast cancer				0.002
Right	420	604	1.00	
Left	543	601	1.32	

Darby, S. C., (2013) *NEJM* **368**(11): 987-998

Clinical outcome

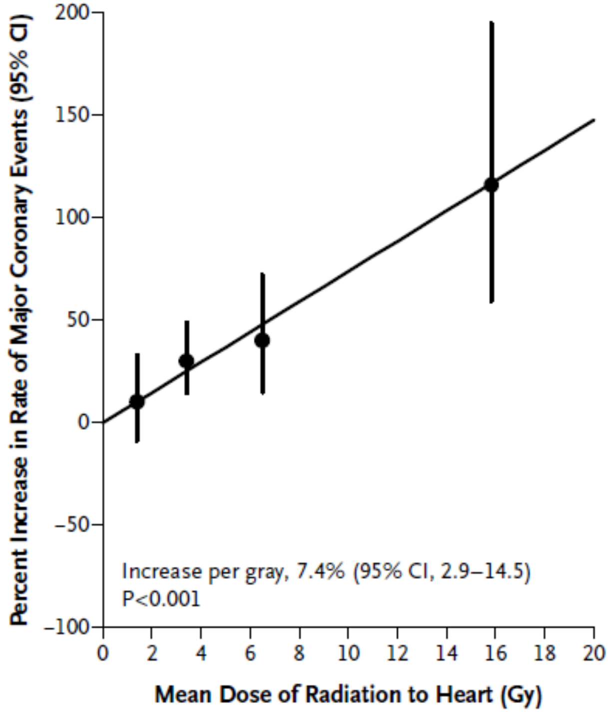
Risk Factors

Factors associated with subsequent coronary event				<0.001
No known cardiac risk factors	353	600	1.00	
History of ischemic heart disease‖	109	38	6.67**	
Risk factors other than ischemic heart disease††	458	527	1.96**	
Unknown	43	40	1.23	
History of circulatory disease other than ischemic heart disease‡‡				<0.001
No	536	845	1.00	
Yes	265	269	1.88	
Unknown	53	53	1.04	
History of diabetes§§				<0.001
No	704	1056	1.00	
Yes	55	29	3.23	
Unknown	95	82	1.19	
History of COPD§§				<0.001
No	736	1076	1.00	
Yes	15	6	6.33	
Unknown	103	85	1.24	

Darby, S. C., (2013) *NEJM* **368**(11): 987-998

Clinical outcome

Effect of radiotherapy



7.4% for each increase of 1 Gy in the mean radiation dose to the heart (P<0.001)

Increase continues for at least 20 years

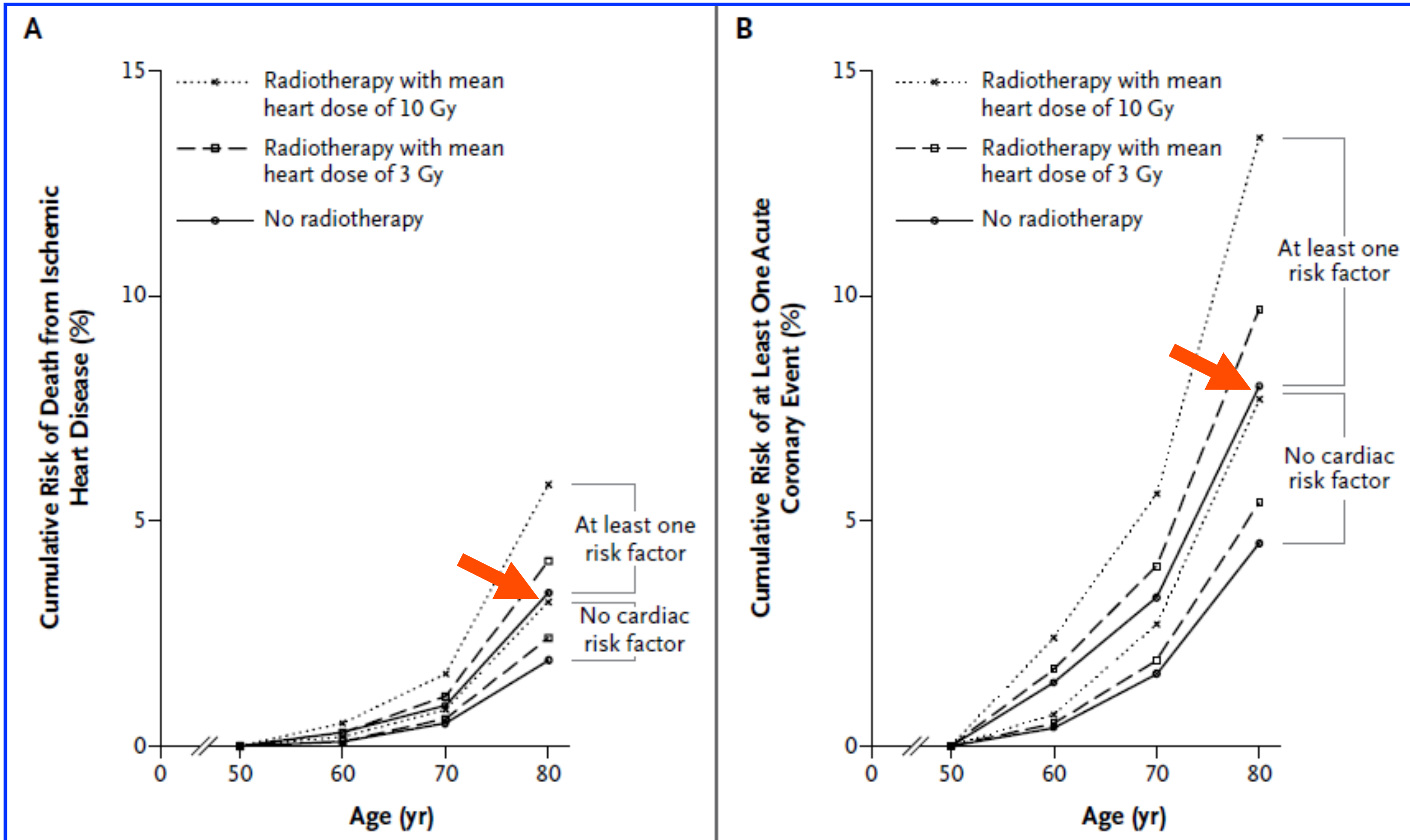
Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

Time since Radiotherapy*	No. of Case Patients	No. of Controls	Increase in Rate of Major Coronary Events (95% CI)†
			% increase/Gy
0 to 4 yr	206	328	16.3 (3.0 to 64.3)
5 to 9 yr	216	296	15.5 (2.5 to 63.3)
10 to 19 yr	323	388	1.2 (−2.2 to 8.5)
≥20 yr	218	193	8.2 (0.4 to 26.6)
0 to ≥20 yr	963	1205	7.4 (2.9 to 14.5)

Darby, S. C., (2013) *NEJM* **368**(11): 987-998

Clinical outcome

Effect of radiotherapy



Darby, S. C., (2013) *NEJM* **368**(11): 987-998

SHORT COMMUNICATION

BJC

British Journal of Cancer (2013) 108, 179–182 | doi: 10.1038/bjc.2012.575

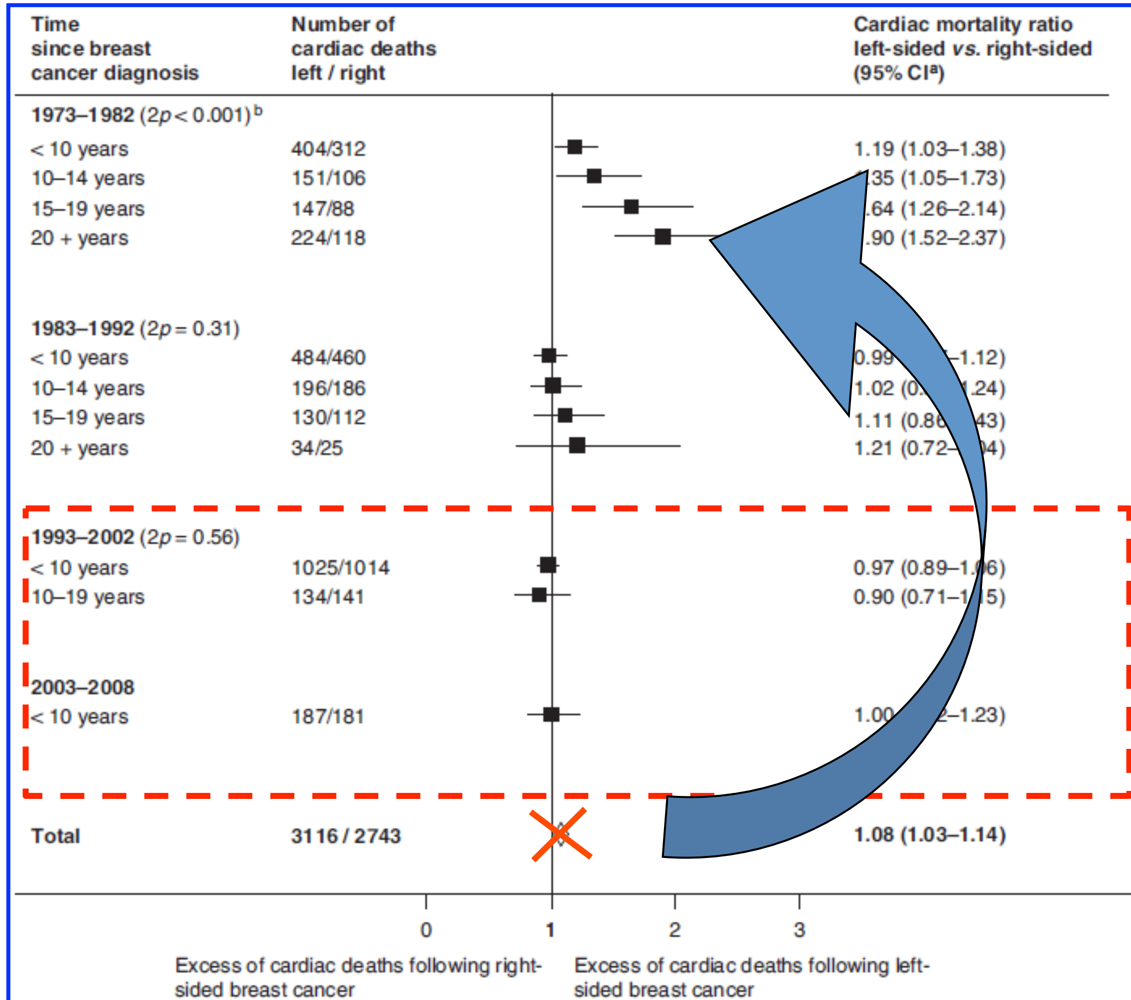
Keywords: epidemiology; breast cancer radiotherapy; radiation-related heart disease; radiation-related lung cancer; long-term effects; mortality

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

558.871 women recorded with breast cancer during 1973–2008 in the SEER

Excess of cardiac deaths for women receiving RT at left-sided breast

RT after 1983 → little evidence of any radiation-related increase in heart disease mortality



Henson, K. E., (2013) *British J Cancer* **108**, 179–182

Clinical outcome

Clinical Investigation: Breast Cancer

Long-term Cardiac Mortality After Hypofractionated Radiation Therapy in Breast Cancer

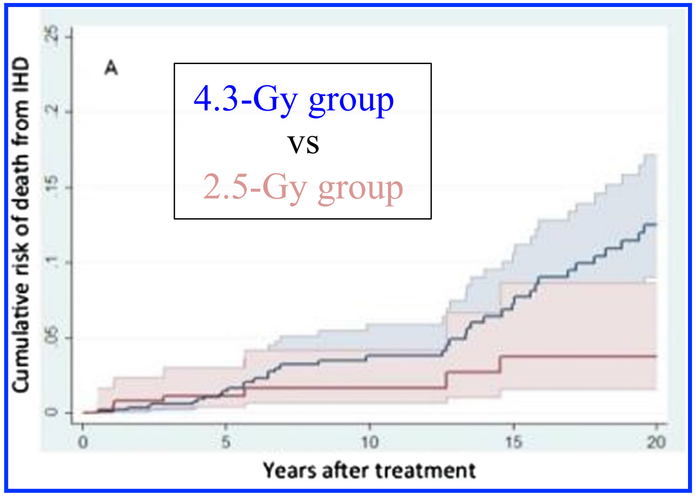
Two ***fractionation patterns*** of radiation therapy: 4.3 Gy x 10 fr or 2.5 Gy x 20 fr

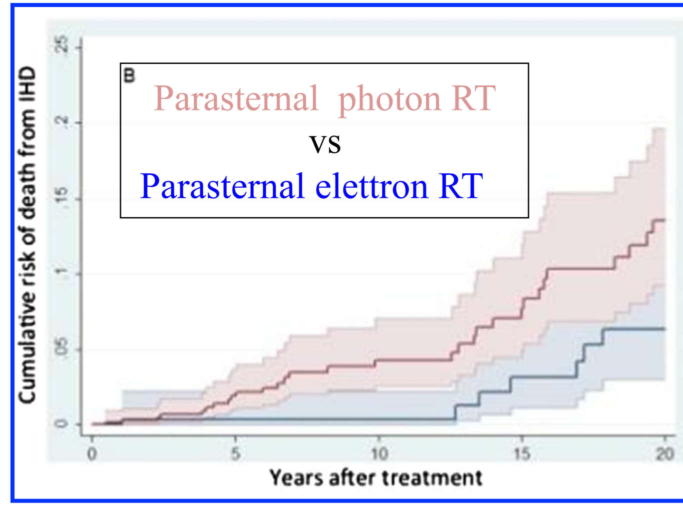
1107 and **459** ***eligible patients*** in the 2 groups

Tjessem, K. H., (2013) *IJROBP* **87**(2): 337-343

Clinical outcome

Hypofractionation





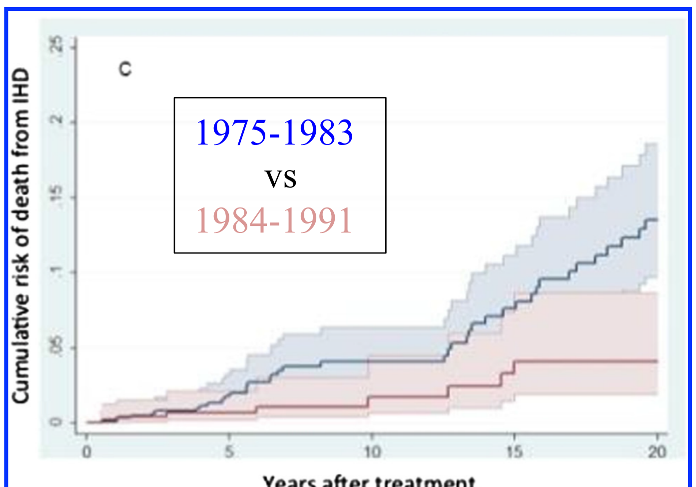


Table 4 Multivariate Cox regression analysis of treatment parameters and risk of death resulting from ischemic heart disease

	Ischemic heart disease		
Treatment variable	HR	95% CI	*P* Value
4.3 Gy vs 2.5 Gy	2.90	0.97-8.76	.057
Photon beams vs no parasternal radiation	0.70	0.26-1.88	.695
Electron beams vs no parasternal radiation	0.34	0.11-1.04	.336

Abbreviations: CI = confidence interval; HR = hazard ratio.

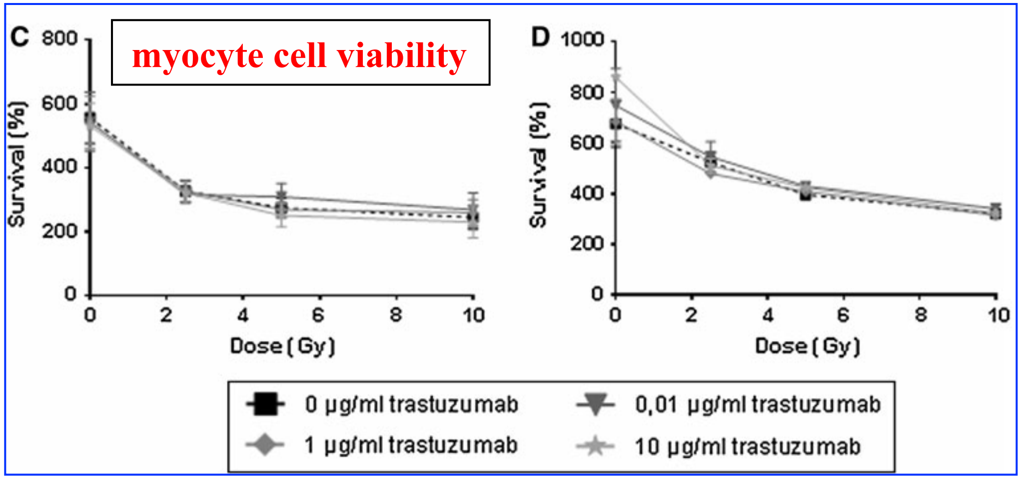
Tjessem, K. H., (2013) *IJROBP* **87**(2): 337-343

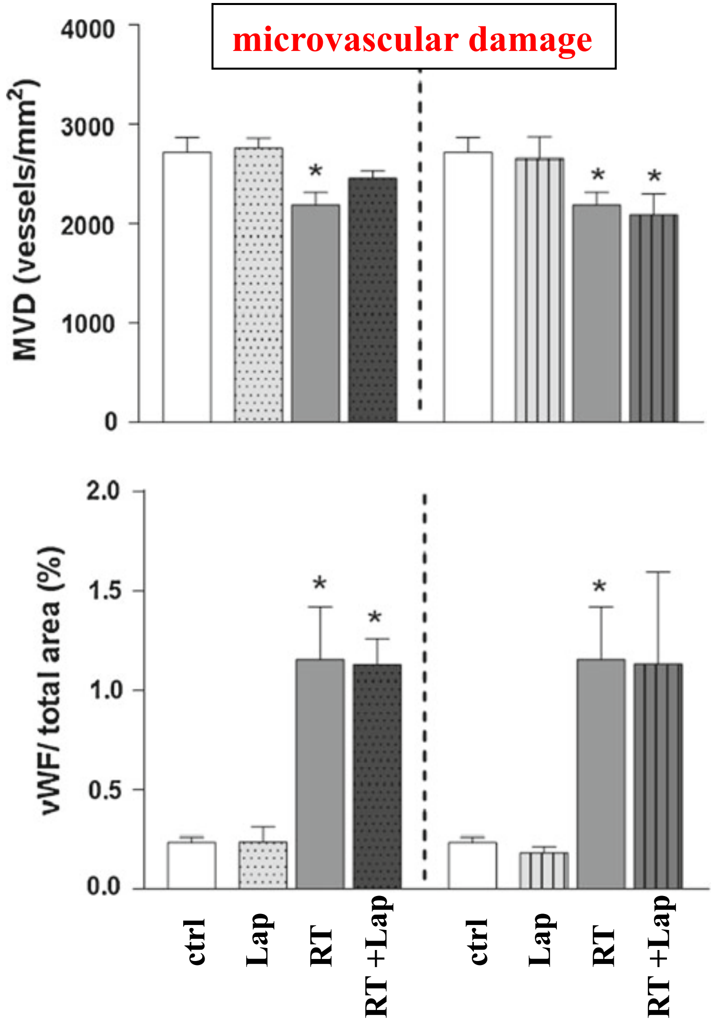
Radioterapia nel trattamento del carcinoma mammario e cardiotossicità

Un problema da quantificare

Clinical outcome

Influence of ErbB2 blocking agents





In combination with irradiation or anthracyclines:

Not decrease *myocyte cell viability* in vitro

Not enhance *cardiac damage* in mice.

Inhibit the *radiation-induced inflammatory* responses

Seemann I., (2013) *Breast Cancer Res Treat* **141:** 385-395

Monitoring

Echocardiography-SRI (strain rate imaging): detection of subclinical RT-induced cardiotoxicity

75 women (51 left-sided and 24 right-sided) receiving adjuvant RT to the breast/chest wall and regional lymph nodes

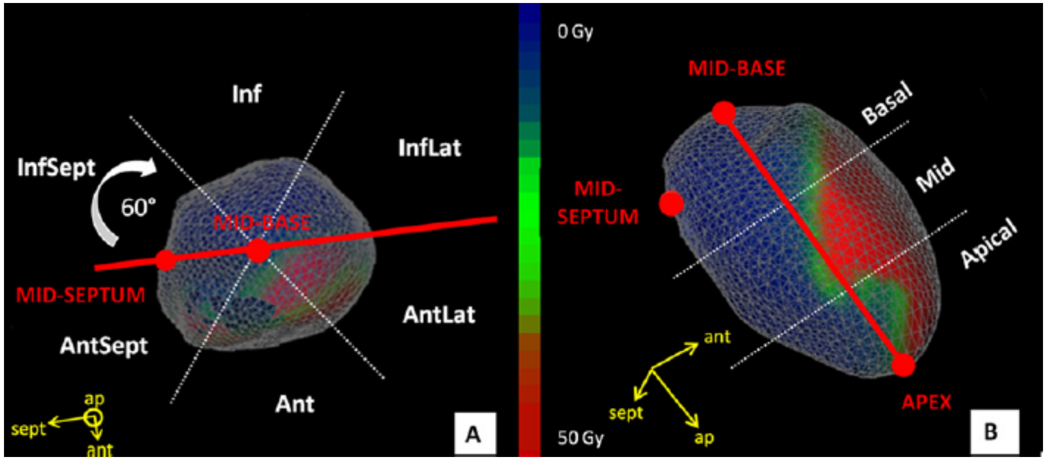
Table 2 Heart dose-volume and NTCP data

Parameter	Left-sided (n=51)	Right-sided (n=24)
Heart		
Mean dose (Gy)	9 ± 4	4 ± 4
V_{30} (%)	7 ± 5	3 ± 4
NTCP (%)	1.8 ± 1.7	0.8 ± 1.4
Left ventricle		
Mean dose (Gy)	9 ± 4	1 ± 0.4
V_{30} (%)	8 ± 7	0 ± 0
Mean dose by location (Gy)		
Anteroseptal wall	14 ± 9	-
Anterior wall	25 ± 14	-
Anterolateral wall	15 ± 11	-
Inferolateral wall	4 ± 3	-
Inferior wall	3 ± 3	-
Inferoseptal wall	5 ± 4	-
Apical segments	10 ± 12	-
Mid segments	11 ± 12	-
Basal segments	12 ± 11	-

Abbreviations: NTCP = normal tissue complication probability; V_{30} (%) = percent of total volume receiving 30 Gy.
Data are given as mean ± standard deviation.

Echocardio with SRI: before RT, immediately after RT, and 8 and 14 months after RT

TnI levels: on the first and last day of RT

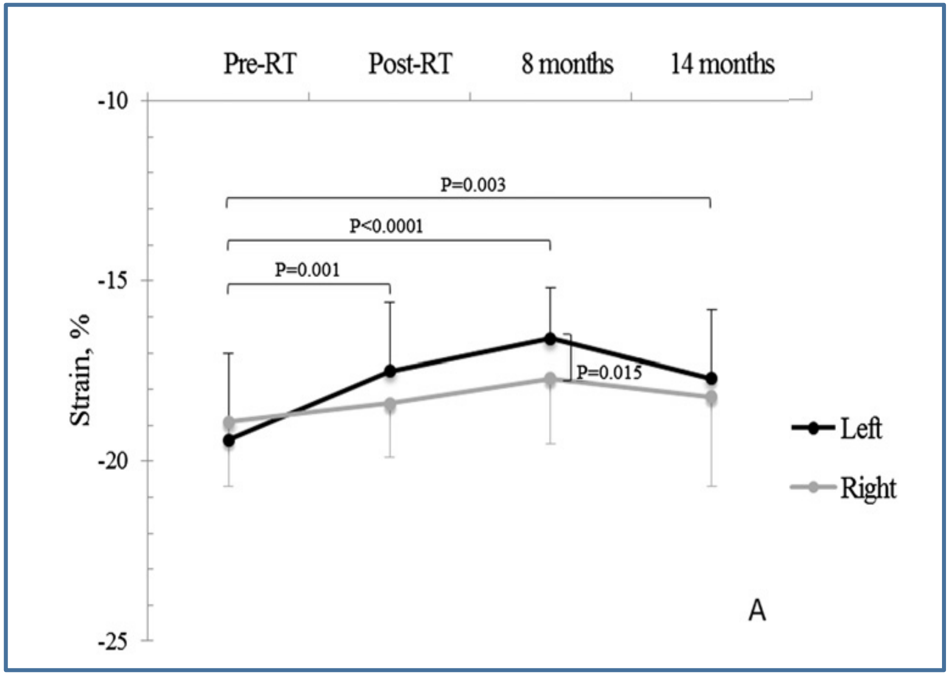


Erven, K., (2013) *IJROBP* **85**(5): 1172-1178

Monitoring

Echocardiography-SRI (strain rate imaging): detection of subclinical RT-induced cardiotoxicity

No significant decrease in ***conventional echocardiography*** parameters for systolic or diastolic function in either left- or right-sided



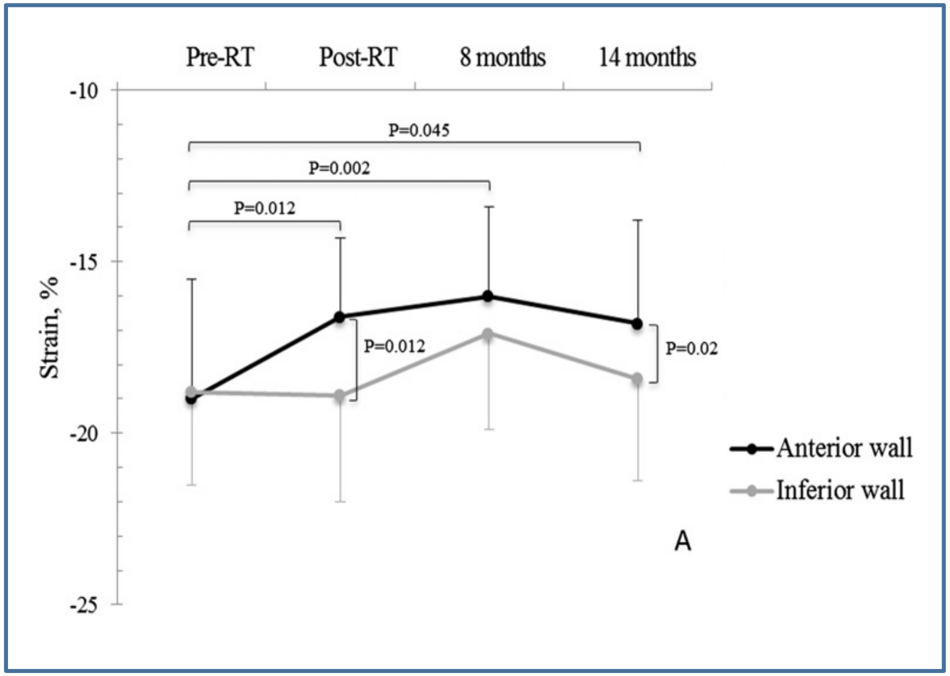
A significant decrease in ***SRI*** for left-sided patients but not for right-sided patients

The largest decrease in SRI: 8 months after RT

Erven, K., (2013) *IJROBP* **85**(5): 1172-1178

Monitoring

Echocardiography-SRI (strain rate imaging): detection of subclinical RT-induced cardiotoxicity



Strain in the anterior segments was ***significantly decreased*** at all post-RT time

For inferior segments ***no significant changes*** after RT

SRI can identify ***reductions in LV function*** **immediately after RT** that are not detectable by conventional echocardiographic

Univariate analysis

No significant correlations with use of trastuzumab, cardiac risk factors.

Only a **nearly significant** with the maximal LV dose.

Erven, K., (2013) *IJROBP* **85**(5): 1172-1178

Volume delineation

Heart contouring variations

Danish consensus on delineation of CTVs and OARs in adjuvant breast RT

Heart contouring atlas: Feng M, et al . Int J Radiat Oncol Biol Phys 2011; 79: 10 – 8

Dice similarity coefficient (DSC): to evaluate the delineation agreement before and after the consensus

Table III. Mean and ranges of DSC before and after consensus.

Volume	Consensus volume (ml)	Mean DSC (range) Before consensus	Mean DSC (range) After consensus
Breast	1247	0.93 (0.89–0.96)	0.95 (0.93–0.96)
Boost	40	NA	0.75 (0.60–0.89)
Internal mammary LN	15	0.59 (0.32–0.72)	0.71 (0.63–0.81)
Axillary LN level I	108	0.65 (0.59–0.75)	0.70 (0.60–0.77)
Axillary LN level II	32	0.56 (0.35–0.69)	0.76 (0.67–0.84)
Axillary LN level III	17	0.56 (0.39–0.73)	0.74 (0.66–0.82)
Periclavicular LN	47	0.41 (0.34–0.56)	0.56 (0.43–0.73)
Interpectoral LN	33	0.54 (NA)	0.66 (0.55–0.78)
Heart	731	0.91 (0.88–0.94)	0.94 (0.90–0.96)

Guidelines improve inter-delineator agreement

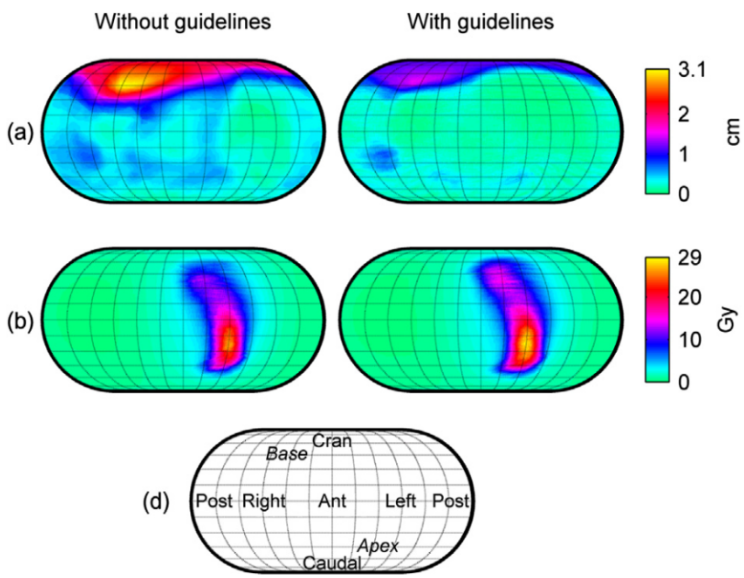
Nielsen M.H., (2013) *Acta Oncologica;* **52**: 703–710

Volume delineation

Heart and left anterior descending coronary artery

Nine observers from five centres delineated the heart and LADCA on 15 patients

The delineations were carried out twice, first without guidelines and then with a set of common guidelines



Major inter-observer variation **at the base of the heart**.

Estimated dose: *modest interobserver variation*.

Guidelines significantly *reduced the variation* in heart delineations

Dose to the **LADCA** was subject to major variation, not reduced by guidelines.

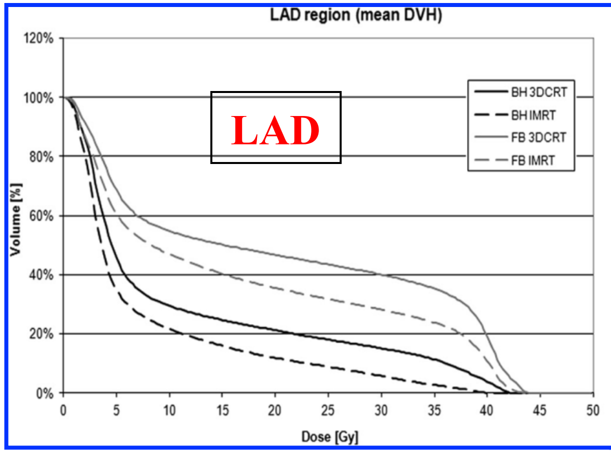
Lorenzen E.L., (2013) *Radiotherapy and Oncology* **108:** 254–258

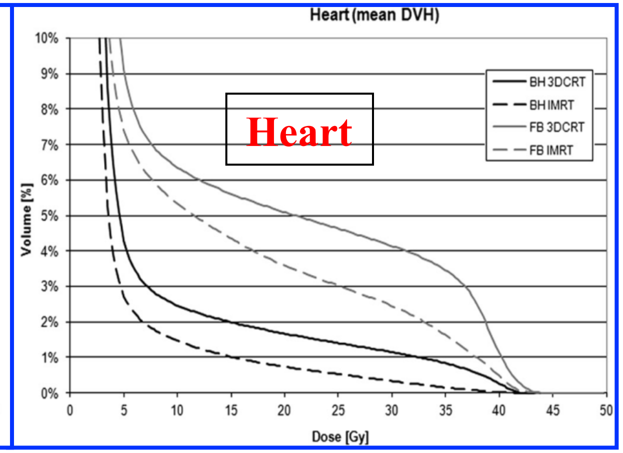
Radioterapia nel trattamento del carcinoma mammario e cardiotossicità

Un problema da evitare

RT techniques

IMRT and DIBH

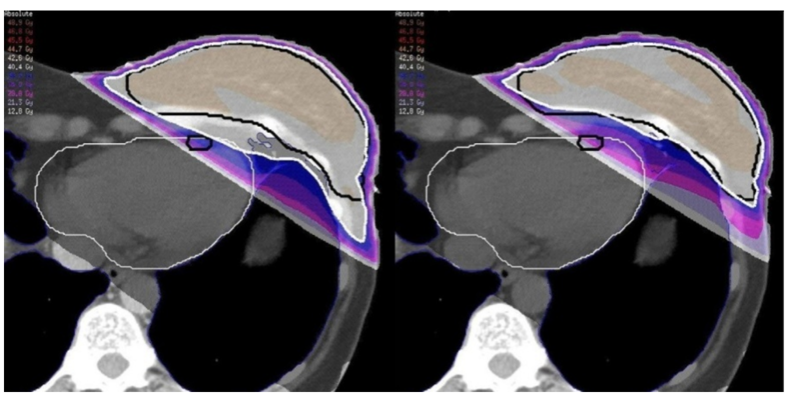




Twenty patients

Four treatment plans:

FB 3D-CRT; FB IMRT; BH 3D-CRT; BH IMRT.



DIBH in left-sided breast cancer RT leads to a ***significant dose reduction*** in the *heart* and the *LAD-region*

IMRT enables an ***additional dose reduction*** in these critical organs

Mast M.E., (2013) *Radioth Oncol;* **108**: 248–253

RT techniques

IMRT techniques (only for small breast)

20 patients; 5 different *radiotherapy techniques*: TW, FIF, T-IMRT, 7-IMRT, VMAT

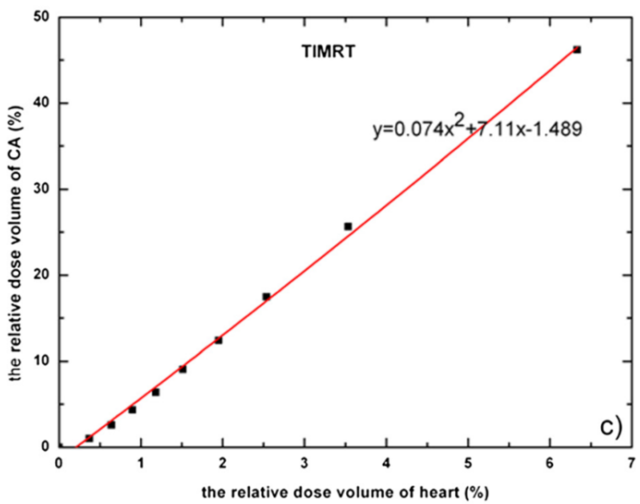


Table 4 Comparison of the PRV-heart dose parameters in five plans ($\bar{x} \pm d$)

Parameters	TW	FIF	T-IMRT	7-IMRT	VMAT
D_{mean}(Gy)	3.7 ± 2.0^{Ab}	3.2 ± 1.9^{A}	2.2 ± 1.0^{Aa}	4.4 ± 1.9^{Ab}	4.6 ± 1.7^{Ab}
V_5 (%)	10.2 ± 6.0^{A}	8.9 ± 5.9^{A}	6.3 ± 3.6^{A}	26.2 ± 21.1^{B}	26.1 ± 15.1^{B}
V_{10} (%)	7.5 ± 5.0^{Aa}	6.1 ± 4.8^{A}	3.5 ± 2.4^{Ab}	6.8 ± 5.4^{Aa}	6.9 ± 4.9^{Aa}
V_{20} (%)	5.6 ± 4.2^{A}	4.3 ± 4.0^{A}	2.0 ± 1.7^{Bb}	2.1 ± 2.1^{Bb}	2.5 ± 2.4^{Ba}
V_{30} (%)	4.2 ± 3.5^{A}	3.2 ± 3.3^{A}	1.2 ± 1.3^{B}	1.0 ± 1.3^{B}	1.1 ± 1.5^{B}
V_{40} (%)	3.0 ± 2.7^{A}	2.0 ± 2.2^{A}	0.6 ± 0.9^{B}	0.3 ± 0.7^{B}	0.4 ± 1.0^{B}

T-IMRT reduced radiation dose exposure to heart

VMAT is *not recommended* for left-sided breast cancer treatment

DVH of the heart can be used to *predict DVH of the coronary artery*

Jin J.H., (2013) *Radiation Oncol;* **8**: 89–253

Radioterapia nel trattamento del carcinoma mammario e cardiotossicità

Un problema reale

Fractionation, Volumes, Other risk factors

Da quantificare

Early diagnosis, dose evaluation accuracy

Da evitare

New techniques →clinical impact → clinical governance