III Zoom Journal Club 2013

To discuss:
"Breast radiotherapy and cardiotoxicity"

Marco Trovò

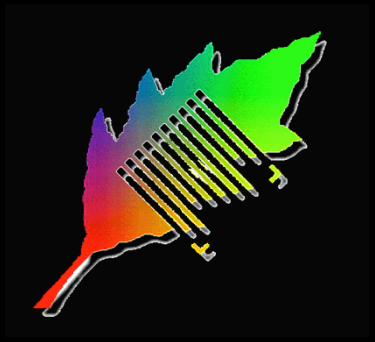
CRO - Aviano

Bologna, 21 Febbraio 2014

Un problema reale?

- Fisiopatologico / Teorico

- Clinico / Pratico



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journal homepage: www.clinicaloncologyonline.net

Overview

Understanding Radiation-induced Cardiovascular Damage and Strategies for Intervention

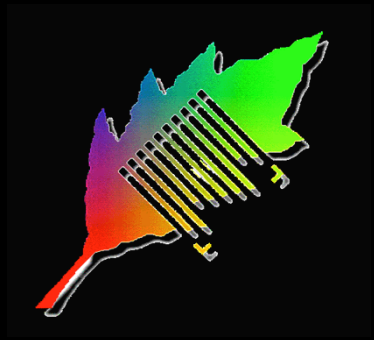
F.A. Stewart *, I. Seemann *, S. Hoving *, N.S. Russell †

* *Division of Biological Stress Response, The Netherlands Cancer Institute, Amsterdam, The Netherlands*
† *Division of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands*

Damage of endothelial cells

1. → Inflammatory process
2. → promoting cell senescence via damage to telomeres

Cardiomiopaty, Valvulopaty, Coronary Artery Disease, and Pericardial Disease.



Cardiovascular Complications of Radiotherapy

Michael S. Lee, MD[a,b,*], Will Finch, MD[a,b], and Ehtisham Mahmud, MD[a,b]

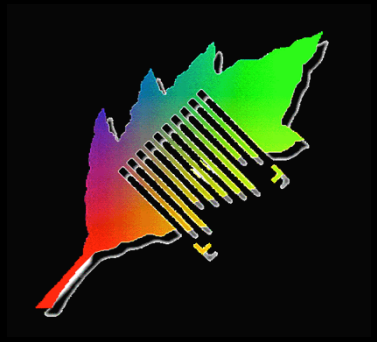
Dose-dependent relation with degree of cardiac injury and radiation

Cardiomiopaty, Valvulopaty and Pericarditis: Doses > 30 Gy

Un problema reale?

- Clinico / Pratico

Un problema da quantificare !

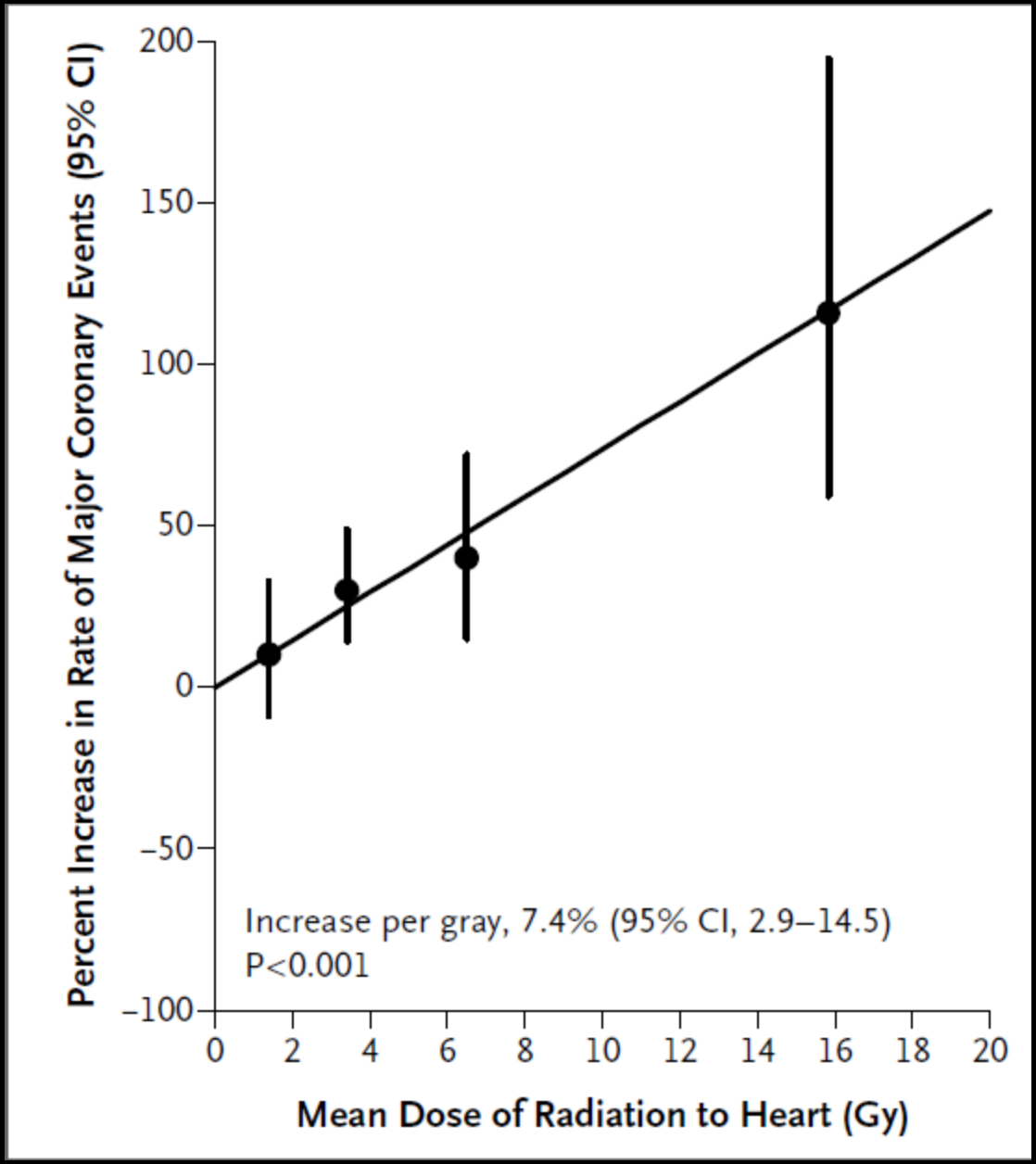


The NEW ENGLAND JOURNAL of MEDICINE

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.


Percent Increase in Rate of Major Coronary Events (95% CI)
200
150
100
50
0
−50
−100
0
2
4
6
8
10
12
14
16
18
20
Mean Dose of Radiation to Heart (Gy)
Increase per gray, 7.4% (95% CI, 2.9–14.5)
P<0.001

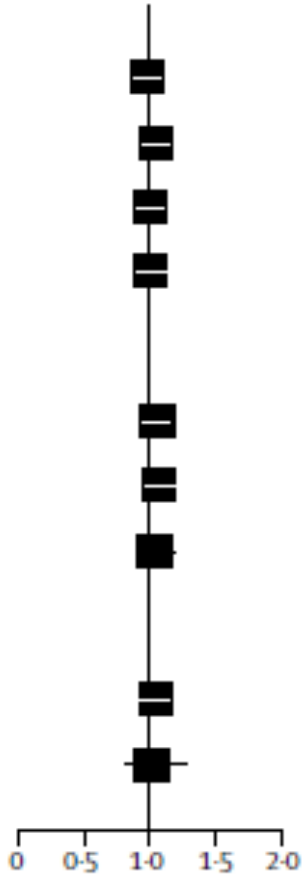
Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300 000 women in US SEER cancer registries

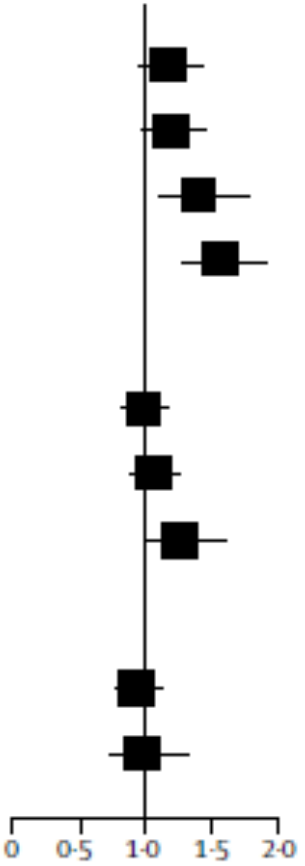
Sarah C Darby, Paul McGale, Carolyn W Taylor, Richard Peto

Breast Cancer RT regimens of 70s and 80s increased mortality from hearth disease 10-20 years afterwards.

Lancet Oncol 2005

Years from breast cancer diagnosis to cardiac death	No radiotherapy		Radiotherapy	
	Cardiac deaths left/right	Cardiac mortality ratio, left-sided vs right-sided (95% CI)	Cardiac deaths left/right	Cardiac mortality ratio, left-sided vs right-sided (95% CI)
Diagnosed 1973–82				
<5 years	717/679	0·98 (0·89–1·09)	230/180	1·19 (0·98–1·45)
5–9	673/614	1·04 (0·93–1·15)	189/145	1·21 (0·97–1·50)
10–14	469/441	1·00 (0·87–1·13)	157/106	1·42 (1·11–1·82)
≥15	515/480	1·01 (0·89–1·15)	234/145	1·58 (1·29–1·95)
Diagnosed 1983–92				
<5 years	880/785	1·06 (0·96–1·16)	245/227	1·00 (0·84–1·20)
5–9	815/729	1·07 (0·97–1·18)	249/218	1·08 (0·90–1·29)
≥10	390/361	1·04 (0·90–1·20)	144/108	1·27 (0·99–1·63)
Diagnosed 1993–2001				
<5 years	567/508	1·05 (0·93–1·18)	225/226	0·95 (0·79–1·14)
5–9	144/136	1·02 (0·81–1·29)	83/79	0·99 (0·73–1·35)





Lancet Oncol 2005

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]

[1]*Clinical Trial Service Unit (CTSU), University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK*

558.000 breast cancer patients

SEER database 1973-2008

Cardiac mortality left-sided vs. right-sided

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

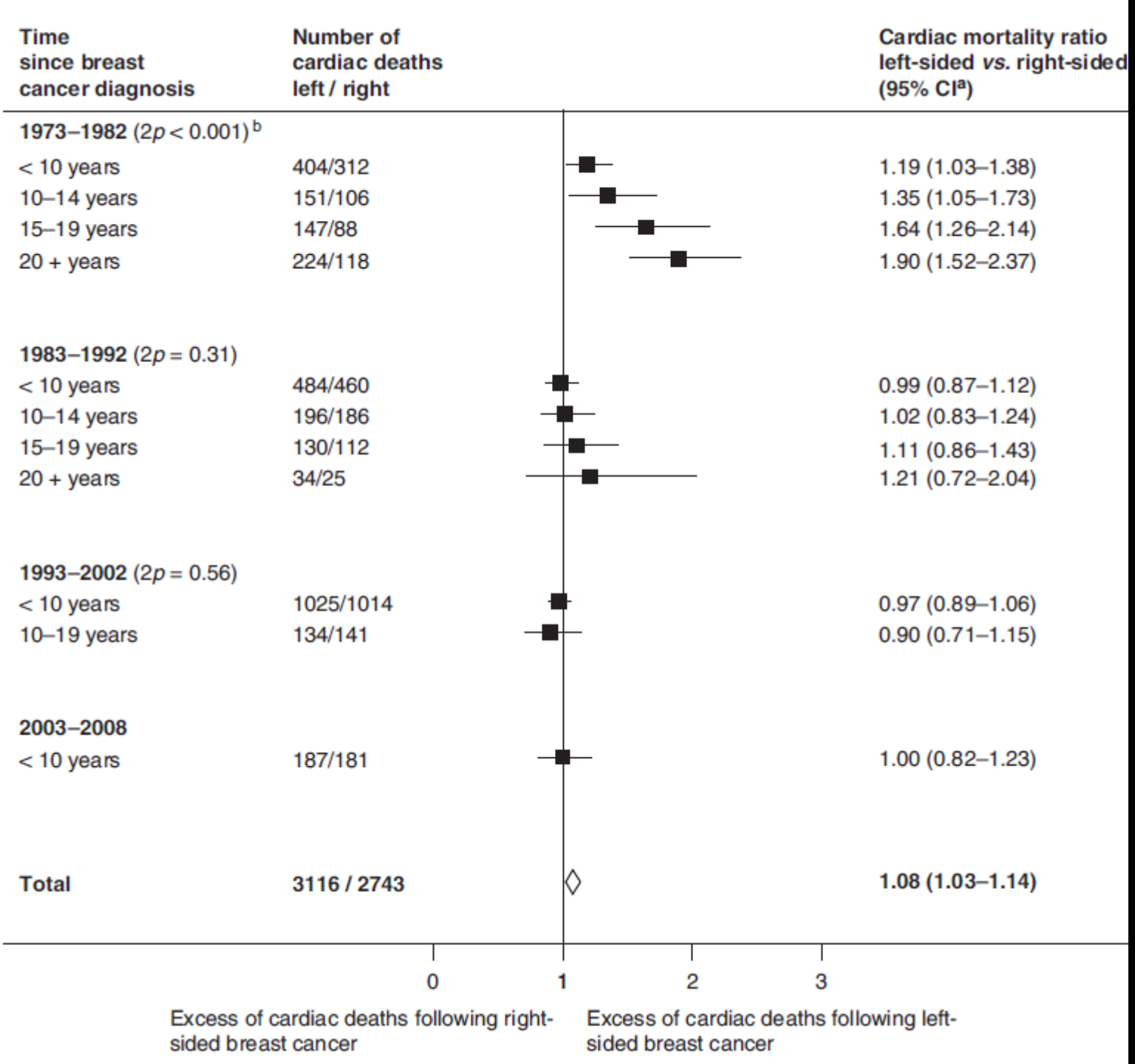
K E Henson*[,1], P McGale[1], C Taylor[1] and S C Darby[1]

[1]*Clinical Trial Service Unit (CTSU), University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK*

Patients receiving NO RT: mortality for hearth disease did not differ between left-sided vs. right sided

Patients receiving RT: excess of cardiac deaths in left-sided:
Cardiac mortality ratio = 1.08 (CI 1.03 – 1.14) (p=0.002)

British Journal of Cancer 2012


Time since breast cancer diagnosis
Number of cardiac deaths left / right
Cardiac mortality ratio left-sided vs. right-sided (95% CI[a])
1973–1982 (2p < 0.001)[b]
< 10 years
404/312
1.19 (1.03–1.38)
10–14 years
151/106
1.35 (1.05–1.73)
15–19 years
147/88
1.64 (1.26–2.14)
20 + years
224/118
1.90 (1.52–2.37)
1983–1992 (2p = 0.31)
< 10 years
484/460
0.99 (0.87–1.12)
10–14 years
196/186
1.02 (0.83–1.24)
15–19 years
130/112
1.11 (0.86–1.43)
20 + years
34/25
1.21 (0.72–2.04)
1993–2002 (2p = 0.56)
< 10 years
1025/1014
0.97 (0.89–1.06)
10–19 years
134/141
0.90 (0.71–1.15)
2003–2008
< 10 years
187/181
1.00 (0.82–1.23)
Total
3116 / 2743
1.08 (1.03–1.14)
0
1
2
3
Excess of cardiac deaths following right-sided breast cancer
Excess of cardiac deaths following left-sided breast cancer

The NEW ENGLAND JOURNAL of MEDICINE

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

1. Inclusion criteria considered patients treated between 1958 and 2001!
2. Without specifying how many patients per time period.

3. If manual planning: doses to the heart were estimated.

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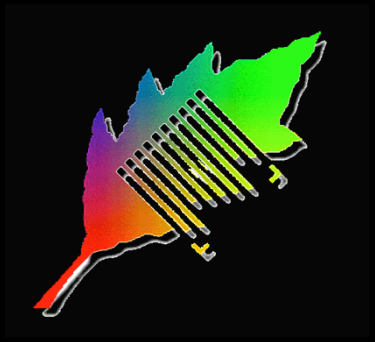
ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

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

1. This study did not compared the risk left vs. right

2. This is a case-control study: dose not permit estimation of ***absolute risk***!

Un problema da evitare …



Factor influencing the Mean Heart Dose:

-Prescription dose

-**RT field** (Target)

-The use of internal mammary RT has declined since the 80's

-RT technique

-Introduction of 3D-Conformal RT (mid 80s) and IMRT

PLENARY

1 Ten-year Results of a Randomized Trial of Internal Mammary Chain Irradiation after Mastectomy

P. Romestaing[1], A. Belot[2], C. Hennequin[3], J. Bosset[4], P. Maingon[5], J. Dubois[6], N. Bossard[2], J. Gerard[7]

[1]Centre De Radiothérapie Charcot, Ste Foy Les Lyon, France, [2]Service De Biostatistiques Des Hospices Civils De Lyon, Lyon Cedex, France, [3]Service De Radiothérapie Hopital St. Louis, Hopitaux De Paris, France, [4]Service De Radiothérapie, Besançon, France, [5]Service De Radiothérapie, Dijon, France, [6]Service De Radiothérapie, Montpellier, France, [7]Service De Radiothérapie, Nice, France

Purpose/Objective(s): To evaluate the impact of internal mammary chain irradiation (IMC-RT) on long-term survival in breast cancer patients treated with mastectomy.

Materials/Methods: Multicentric randomized Phase III trial comparing chest wall, axillary, and supra-clavicular irradiation with or without IMC-RT in newly diagnosed Stage I and II breast cancers. Inclusion criteria: patients under 76-years-old with positive axillary nodes or internal/central tumor location whatever pN. Stratification was done by center, nodal status, and tumor location (internal/central vs. external). The IMC-RT consisted in a combination of photons (12.5 Gy in 5 fractions) and electrons (32.5 Gy in 13 fractions) over 5 weeks. The target field included the first five intercostal spaces. Adjuvant chemotherapy or hormonal treatment was at the discretion of the physician. We planned to include 1,200 patients that allowed us to detect 10% difference in 10-year overall survival.

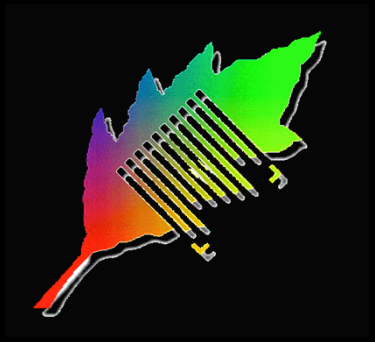
Results: A total of 1,334 patients have been randomized. Mean age was 56.5-years-old, 1,003 (75%) patients had positive lymph nodes. With a median follow-up of 10 years, we observed 535 deaths. Ten-year survival was 62.57% in case of IMC-RT and 59.55% without IMC-RT ($p = 0.8762$ by log–rank test). No difference was obtained in the different subgroups: positive or negative axillary nodes, external vs. central/internal tumors, or according to the different histologic subtypes, adjuvant chemotherapy, or hormonotherapy. Causes of death are known in 422 patients: most of these deaths were due to breast cancer (371); no increase in cardiac toxicity was observed in the IMC-RT group.

Conclusions: Using IMC-RT did not improve overall survival in this large randomized study.

Mean Hearth Dose:
-Prescription dose

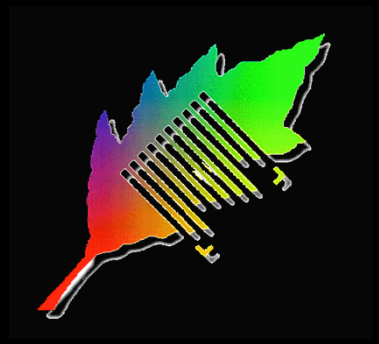
-**RT field** (Target)
-The use of internal mammary RT has declined since the 80's

-RT technique
-Introduction of 3D-Conformal RT (mid 80s) and IMRT

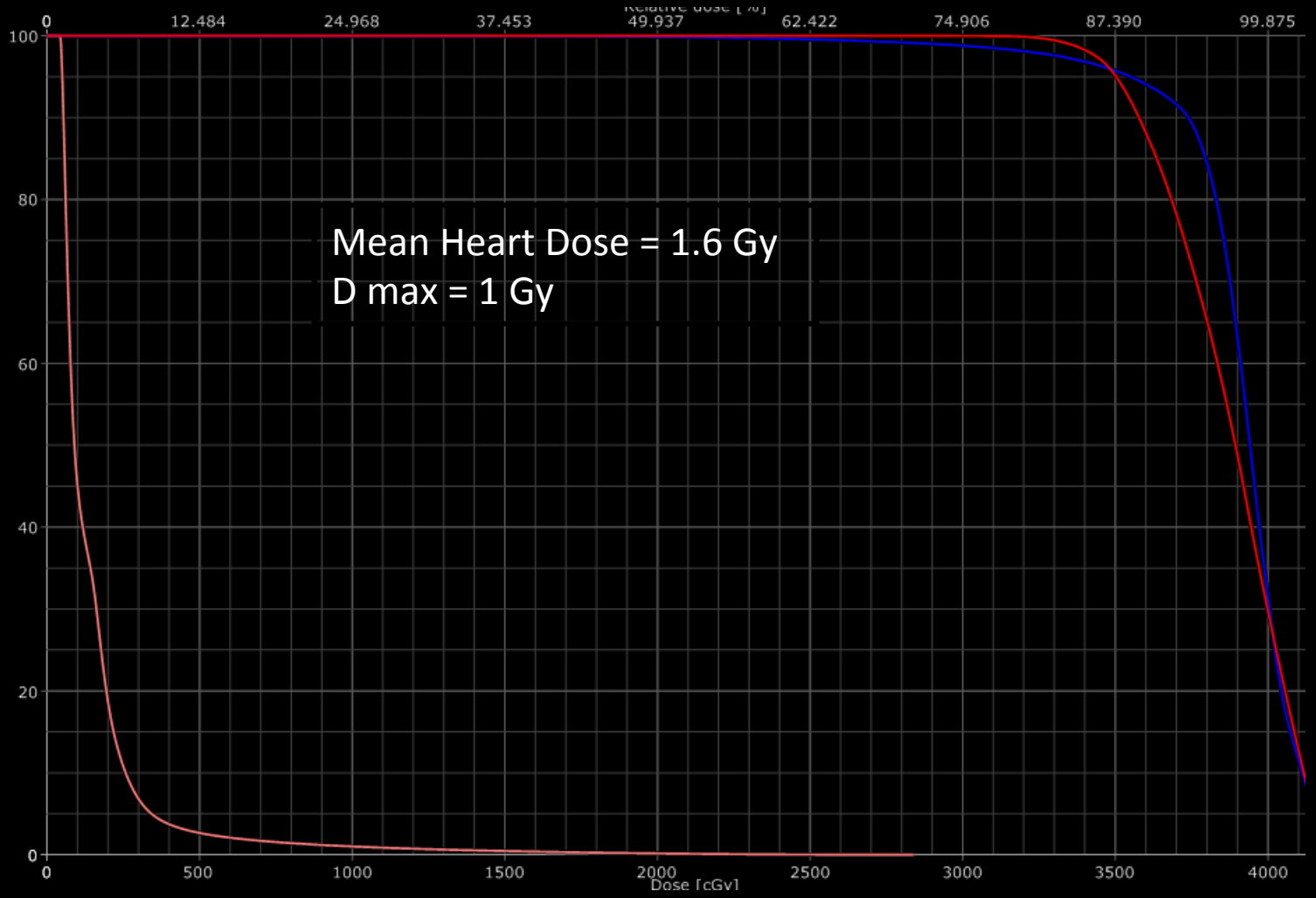


Is there an increased risk of local recurrence under the heart block in patients with left-sided breast cancer?

Raj KA et al.. Cancer J. 2006 Jul-Aug;12(4):309-17.

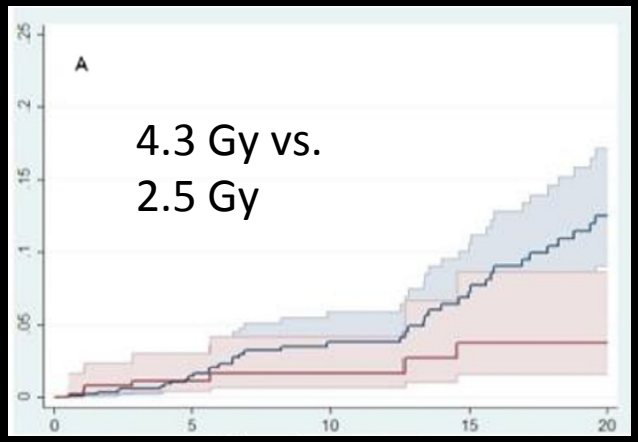


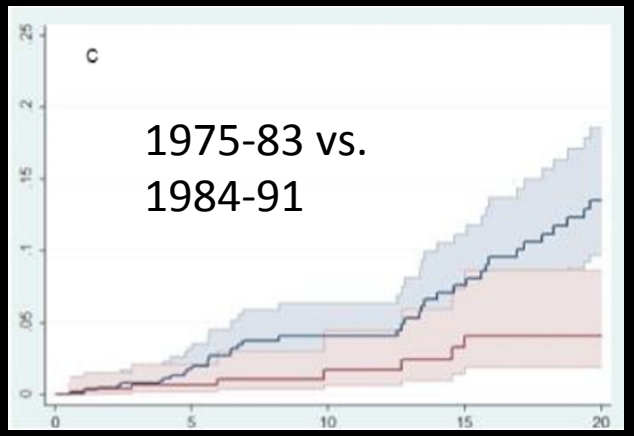
3D –Conformal RT



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

Kristin Holm Tjessem, MD,* Safora Johansen, PhD,† Eirik Malinen, PhD,‡ Kristin V. Reinertsen, MD, PhD,* Turi Danielsen, PhD,‡ Sophie D. Fosså, MD, PhD,* and Alexander Fosså, MD, PhD*





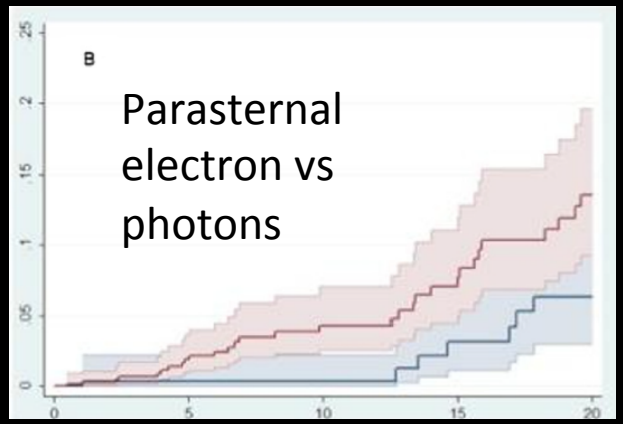


Table 4 Multivariate Cox regression analysis of treatment parameters and risk of death resulting from ischemic heart disease

	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.

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

Kristin Holm Tjessem, MD,* Safora Johansen, PhD,† Eirik Malinen, PhD,‡ Kristin V. Reinertsen, MD, PhD,* Turi Danielsen, PhD,‡ Sophie D. Fosså, MD, PhD,* and Alexander Fosså, MD, PhD*

1. Ipofrazionamento non attuale

2. 90% dei pazienti trattati col frazionamento 4.3 Gy/fr riceveva anche IMN

3. Conferma dell'importanza dell'epoca del trattamento radiante

→ dati non attuali.

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

Kristin Holm Tjessem, MD,* Safora Johansen, PhD,† Eirik Malinen, PhD,‡ Kristin V. Reinertsen, MD, PhD,* Turi Danielsen, PhD,‡ Sophie D. Fosså, MD, PhD,* and Alexander Fosså, MD, PhD*

Table 2 Patient demographics, treatment variables, and causes of death

Characteristic	4.3 Gy × 10	%	2.5 Gy × 20	%	*P* Value
Total number of patients	1107	-	459	-	-
Median age, years (range)	58.8 (23.6-85.3)	-	58.4 (25.6-94.1)	-	.810
Laterality					
Right	500	45.2	225	49.0	.165
Left	607	54.8	234	51.0	-
Median observation time/years (range)					
All patients	4.5 (0.1-20.0)	-	3.9 (0.1-20.0)	-	.043
Surviving patients	20 (20-20)	-	20 (18.2-20)	-	<.001
Stage					
1	212	19.2	75	16.3	-
2	553	50.0	201	43.8	-
3	198	17.9	140	30.5	<.001
4	129	11.7	394	8.5	-
Unknown	15	1.4	4	0.9	-
Field arrangement					
Including parasternal field					
Parasternal and tangential fields	706	63.8	99	21.6	-
Parasternal and fields other than tangential	300	27.1	63	13.7	-
Without parasternal field	-	-	-	-	<.001
Including tangential field	74	6.7	274	59.7	-
Including fields other than tangential	12	1.1	8	1.7	-
Unknown	15	1.3	15	3.3	-
Beam quality (in parasternal field)					
Electrons	246	24.5	114	70.4	<.001
Photons	760	75.5	48	29.6	-
Treatment period					
1977-1983	945	85.4	36	7.8	<.001
1984-1991	162	14.6	423	92.2	-
Total number of deaths	954	86.2	386	84.1	.469

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

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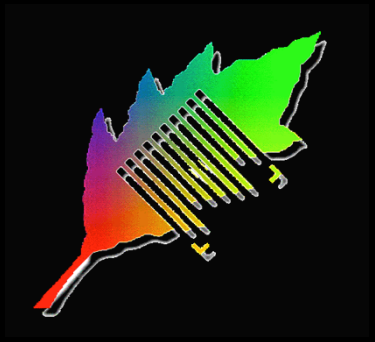
Residual confounding

Table 3 Univariate Cox regression analysis of treatment parameters and risk of death resulting from ischemic heart disease

Treatment variable	Ischemic heart disease		
	HR	95% CI	*P* value
4.3 Gy vs 2.5 Gy	2.37	1.06-5.32	.036
4.3 Gy vs controls	1.59	1.13-2.23	.008
2.5 Gy vs controls	0.78	0.36-1.68	.530
Parasternal field radiation vs no parasternal field radiation	0.915	0.43-1.97	.820
Photon beams vs electron beams	2.56	1.12-5.84	.025
Photon beams vs no parasternal radiation	1.41	0.65-3.08	.383
Electron beams vs no parasternal radiation	0.76	0.54-1.27	.300
Photon beams vs controls	1.79	1.21-2.67	.004
Electron beams vs controls	0.76	0.35-1.64	.480
No parasternal radiation vs controls	0.99	0.48-2.07	.985
Early treatment (1977-1983) vs late treatment (1984-1991)	2.87	1.34-6.17	.006
Early treatment vs controls	1.67	1.18-2.36	.004
Late treatment vs controls	0.74	0.36-1.53	.416
Laterality (left vs right)	0.93	0.52-1.66	.812

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

Un problema da evitare …



Acta Oncologica, 2013; 52: 703–710

informa
healthcare

ORIGINAL ARTICLE: ACTA ONCOLOGICA JUBILEE ARTICLE

Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: National guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group

Table II. Constraints for organs at risk in adjuvant radiotherapy of early breast cancer.

Organ at risk	Normofractionation 2 Gy per fraction/ 5 fractions/week
LADCA	$V_{20Gy} = 0\%$
Heart	$V_{20Gy} = 10\%$, $V_{40Gy} = 5\%$
Ipsilateral lung	$V_{20Gy} = 25\%$ (exclusive periclavicular LN) $V_{20Gy} = 35\%$ (inclusive periclavicular LN) Mean dose < 18 Gy
Spinal cord	Max. 45 Gy
Plexus brachialis	Max. 54 Gy
Maximal dose of CTV	107% = 53.5 Gy
Maximal dose outside PTV	54 Gy

Grazie per l'attenzione !

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