CARDIOTOSSICITA' DA RADIOTERAPIA

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Background

- Radiation Therapy (RT) has contributed to significant improvements in disease-specific survival for patients with early stage Breast Cancer, Hodgkin Lymphoma (HL), and other malignancies involving the thoracic region

- Irradiation of a substantial volume of the heart to a sufficiently high dose can damage virtually any component of the heart, including the pericardium, myocardium, heart valves, coronary arteries, capillaries, and conducting system

- The data on the late cardiovascular toxicity of RT come primarily from survivors of breast cancer and HL, diseases in which RT is a frequent component of the initial management and in which survival is often prolonged. Similar effects may be present in other cancer survivors who receive thoracic RT, although data are more limited.

PATHWAYS IN RADIATION-INDUCED HEART DISEASE

1. Cardiomyocyte

2. Smooth muscle cells

3. Endothelial cells

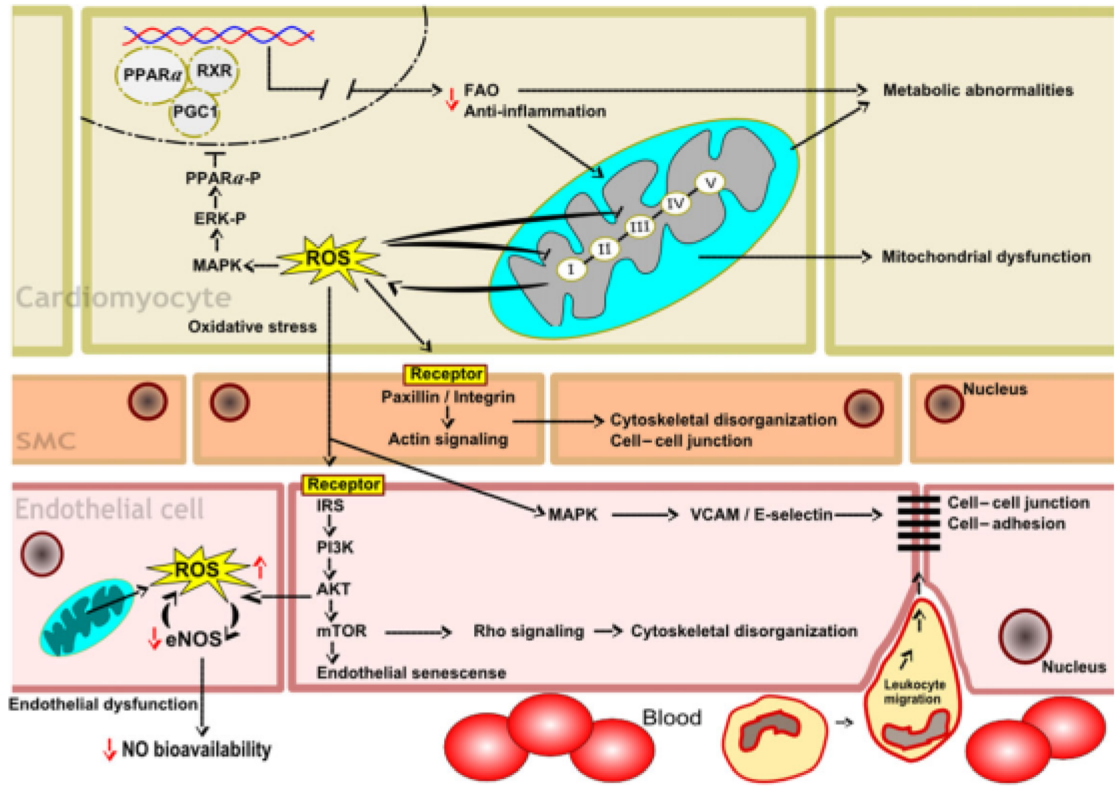


Fig. 1. Proposed model of the biological pathways in cardiomyocytes, smooth muscle cells (SMCs) and endothelial cells involved in radiation-induced heart disease. In cardiomyocytes, the inactivation of PPAR alpha, reduced fatty acid oxidation (FAO), increased inflammatory response, and enhanced production of mitochondrial ROS are indicated. In SMCs, the adverse effects on paxillin/integrin and actin signaling, cytoskeletal organization, and cell–cell junctions are shown. In endothelial cells, the inactivation of PI3K, MAP kinase and Rho signaling pathways, increased cytoskeletal disorganization, decreased NO production and bioavailability, and enhanced leukocyte migration due to increased cell adhesion and loosening of cell–cell junctions are indicated.

Topio. J Radiat Res. 2016 Sep; 57(5): 439–448

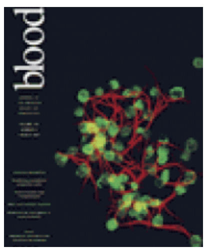
RADIATION-INDUCED HEART DISEASE
Lessons from the past in the era of "modern" radiation therapy

VOLUME 22 · NUMBER 15 · AUGUST 1 2004

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Cardiovascular Status in Long-Term Survivors of Hodgkin's Disease Treated With Chest Radiotherapy

M. Jacob Adams, Stuart R. Lipsitz, Steven D. Colan, Nancy J. Tarbell, S. Ted Treves, Lisa Diller, Nina Greenbaum, Peter Mauch, and Steven E. Lipshultz



Late cardiotoxicity after treatment for Hodgkin lymphoma

Berthe M. P. Aleman,[1] Alexandra W. van den Belt-Dusebout,[2] Marie L. De Bruin,[2] Mars B. van 't Veer,[3] Margreet H. A. Baaijens,[4] Jan Paul de Boer,[5] Augustinus A. M. Hart,[1] Willem J. Klokman,[2] Marianne A. Kuenen,[2] Gabey M. Ouwens,[2] Harry Bartelink,[1] and Flora E. van Leeuwen[2]

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Cancer patients who received therapeutic doses (30-50 Gy in 2 Gy fractions) of thoracic radiotherapy before 2000 have an increased risk of cardiac mortality at >10 years after treatment.

RADIATION-INDUCED HEART DISEASE
Lessons from the past in the era of "modern" radiation therapy

Increased cardiac mortality in Old Studies

Patient enrolment, years	Increase in risk for cardiac death (hazard ratio) in follow-up			
	Up to 10 years	10–14 years	15–19 years	≥ 20 years
1973–1982	*1.19*	*1.35*	*1.64*	*1.90*
1983–1992	0.99	1.02	1.11	1.21
1993–2002	0.97	0.99		no data
2003–2008	1.00	no data	no data	no data

Irradiated patients had a higher rate of cardiac deaths compared to the control group without irradiation. When listing the studies in chronological order, this was only significant in studies that recruited until 1982 (significant risks are highlighted in the table in italics). In studies with recruitment from 1983 to 1992, a very small, not more significant risk resulted after more than 15 years. In subsequent work, increased cardiac mortality was no longer observed (modified from [2]).

Nitsche et al. 2015

RADIATION-INDUCED HEART DISEASE
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The Example of Breast Cancer RT
(Early Breast Cancer Trailists' Collaborative Group data)

Table 2. Data of the EBCTCG, evaluation 2005

Heart dose, range (mean)	Total number of patients	Cardiac events in irradiated patients	Cardiac events in non-irradiated patients	Hazard ratio for annual risk
0–5 Gy (3 Gy)	9,982	2.9%	2.4%	1.08 (n.s.)
5–15 Gy (9 Gy)	7,850	5.4%	3.8%	1.32
> 15 Gy (17 Gy)	2,265	11.0%	6.4%	1.63

Irradiated patients had a higher rate of cardiac deaths. In the low-dose group, this effect was not significant. In the group with higher radiation doses, cardiac events even increased in the control group without irradiation. This can be explained mainly by the fact that high doses of radiation were used in the earliest studies with long follow-up and thus higher cardiac risk became apparent in non-irradiated patients in the control group. As a consequence of the data, one should have an average heart dose of less than 3–5 Gy in modern technology. Under these conditions, there is no significant cardiac risk [3].
n.s. = Not significant.

Nitsche et al. 2015

RADIATION-INDUCED HEART DISEASE
Lessons from the past in the era of "modern" radiation therapy

VOLUME 34 · NUMBER 24 · AUGUST 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

Radiation Dose-Response Relationship for Risk of Coronary Heart Disease in Survivors of Hodgkin Lymphoma

Rosario Mazzola, Niccolò Giaj Levra, and Filippo Alongi
Sacro Cuore Don Calabria Cancer Care Center, Negrar-Verona, Italy

uation. Most of patients analyzed in the study were treated with two-dimensional RT from 1965, which had a large impact on cardiac outcomes. Moreover, radiation charts and simulation radiographs were used to estimate in-field heart volume and mean heart dose without considering patient anatomy. In our opinion, the method seems rather crude. In the modern era of RT, it would be unthinkable to avoid accurate dosimetry using modern algorithms that adjust for tissue inhomogeneities. Thus, although RT allows

standard approach in HL. The use of limited radiation field (involved-field and involved-site RT) allows control of known tumor sites, whereas the use of limited cycles of chemotherapy can eradicate HL cells outside the radiation field. This approach, when compared with chemotherapy alone, has an advantage in disease-free survival.[5] The impact of reduced volumes and doses has been addressed, especially with the integration of modern imaging and advanced techniques for delivery of treatment. In this regard, the

International Journal of Radiation Oncology biology • physics
Official Journal of the American Society for Radiation Oncology ASTRO

Modern Radiation Therapy and Cardiac Outcomes in Breast Cancer

Thus, the main question remains: how can we balance the risk and benefit related to BC irradiation? New technical and technological advances could be helpful to minimize heart exposure. Intensity modulated RT and volumetric modulated arc therapy are potentially able to reduce high doses to the heart (7). Various approaches can contribute to reduce heart doses (active breath control, prone position, and partial breast irradiation), although their benefit has not been clearly defined.

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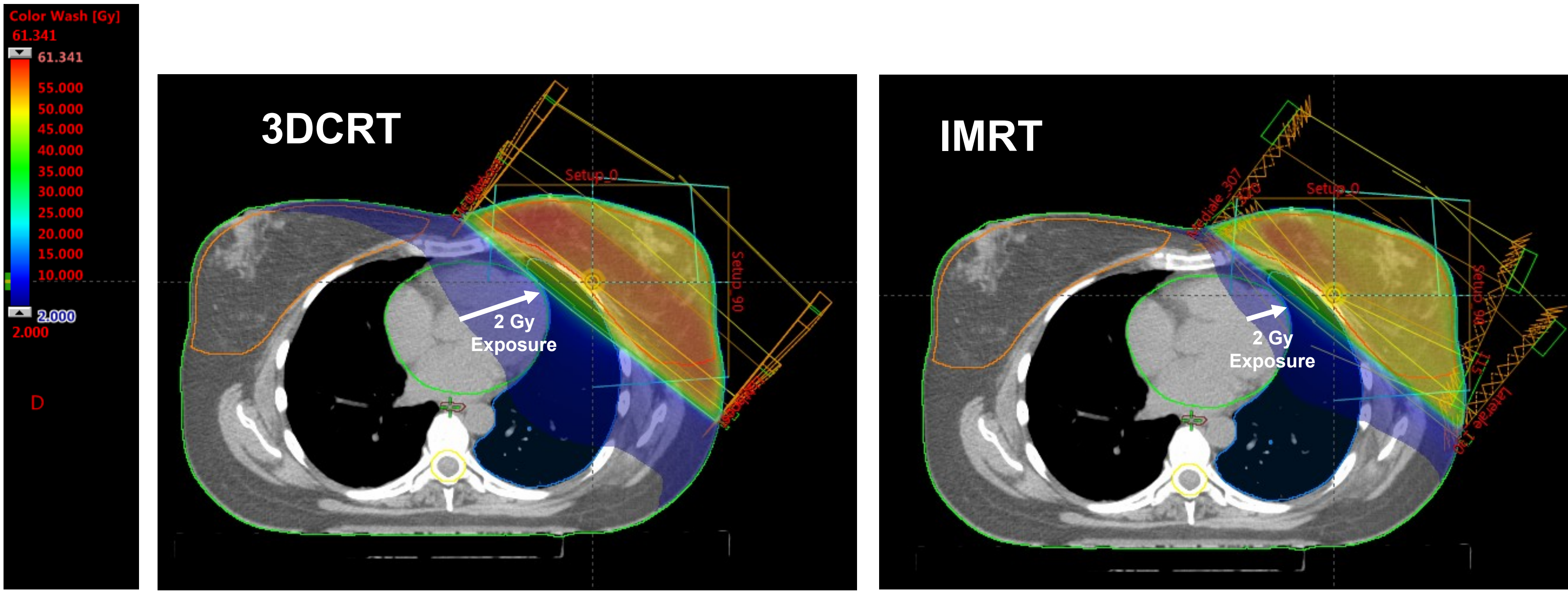
An Example of 3D-conformal Radiotherapy (3DCRT) and Intensity Modulated Radiotherapy (IMRT)



1. Is It possible to estimate a Cut-off value of **radiation-associated heart damage?**

2. How to reduce **radiation-heart exposure?**

3. How to predict **radiation-associated heart damage?**

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1. Is It possible to estimate a Cut-off value of **radiation-associated heart damage?**

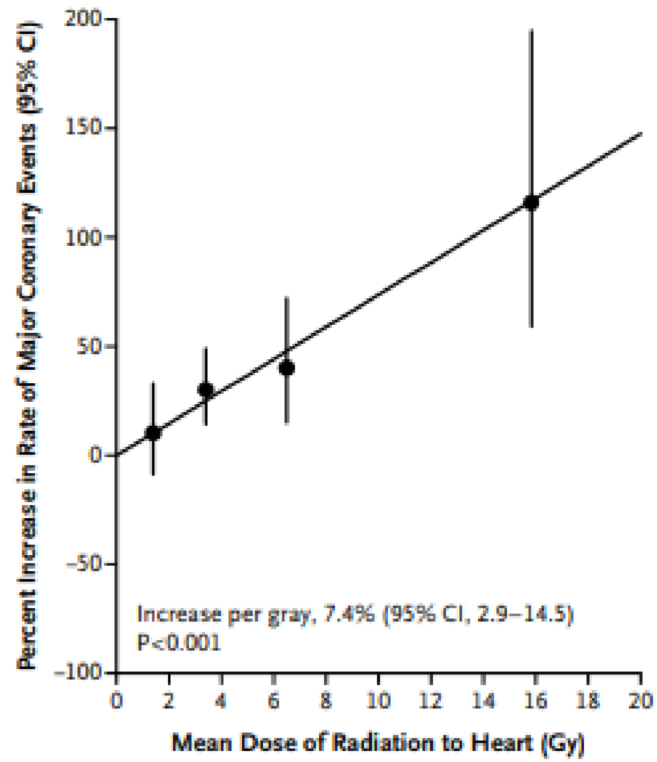
The NEW ENGLAND JOURNAL of MEDICINE

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.

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. The circles show values for groups of women, classified according to dose categories; the associated vertical lines represent 95% confidence intervals. All estimates were calculated after stratification for country and for age at breast-cancer diagnosis, year of breast-cancer diagnosis, interval between breast-cancer diagnosis and first major coronary event for case patients or index date for controls (all in 5-year categories), and presence or absence of a cardiac risk factor. The radiation categories were less than 2, 2 to 4, 5 to 9, and 10 Gy or more, and the overall averages of the mean doses to the heart of women in these categories were 1.4, 3.4, 6.5, and 15.8 Gy, respectively.



1. Is It possible to estimate a Cut-off value of **radiation-associated heart damage?**

Radiotherapy and Oncology 90 (2009) 127–135

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

Cardiac toxicity

Cardiac doses from Swedish breast cancer radiotherapy since the 1950s

Carolyn W. Taylor[a,*], Andrew Nisbet[b], Paul McGale[a], Ulla Goldman[c], Sarah C. Darby[a], Per Hall[d], Giovanna Gagliardi[e]

Table 2
Cardiac doses for Swedish women identified using the Swedish :ancer since 1958, based on i

Decade of radiotherapy	Number of women evaluated	Heart dose (Gy) Left	Heart dose (Gy) Right
1958 and 1959	25	5.1 (2.2)	1.8 (1.6)
1960s	148	4.6 (5.1)	2.1 (1.9)
1970s	93	10.5 (7.2)	4.7 (4.6)
1980s	65	7.0 (5.8)	2.7 (2.1)
1990s	27	3.0 (0.5)	1.9 (0.2)

[a] Biologically effective dose. Doses were calculated for 91% o BED for the other 9% as they on 44% of the women irradiated in the 1950s, 96% of women ithe 1970s and 100% of wom
[b] Left anterior descending coronary artery.
[c] Right coronary artery.
[d] Circumflex coronary artery.

Reductions in mean heart dose from **13.3Gy** in the **1970s,** to **4.7Gy** in the **1990s,** and **2.3Gy** in **2006**

This decrease seems to have resulted in a very low risk of death caused by radiation-induced heart disease (RIHD), at least for women without cardiac risk factors

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Radiol med
DOI 10.1007/s11547-016-0700-z

CrossMark

RADIOTHERAPY

Three-dimensional conformal versus intensity modulated radiotherapy in breast cancer treatment: is necessary a medical reversal?

Alba Fiorentino[1] · Ruggero Ruggieri[1] · Niccolò Giaj-Levra[1] · Gianluisa Sicignano[1] · Gioacchino Di Paola[2] · Stefania Naccarato[1] · Sergio Fersino[1] · Rosario Mazzola[1] · Umberto Tebano[1,3] · Francesco Ricchetti[1] · Filippo Alongi[1]

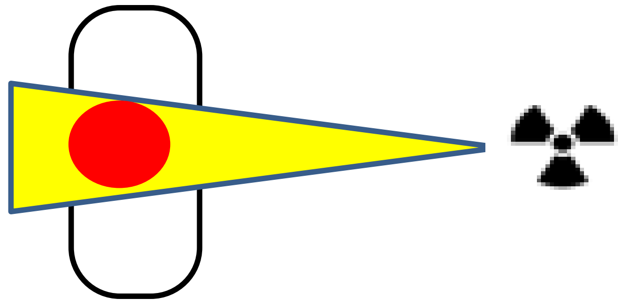
Table 2 Dosimetric parameters for Organs at risk

Heart						
	D_{mean}GY	D_{median}GY	$D_{2\%}$	V_{5Gy}	$V_{10\,Gy}$	$V_{25\,Gy}$
3D-CRT	2.4 ± 1.3	1.8 ± 0.8	11.4 ± 13.4	4.6 ± 6.2	1.4 ± 2.0	0.7 ± 1.2
IMRT	1.2 ± 1.0	0.7 ± 0.5	6.6 ± 6.7	3.2 ± 4.7	1.1 ± 2.3	0.2 ± 0.5
p value	*<0.0001*	*<0.0001*	*0.0117^*	0.0946^	0.3441^	*0.0245^*

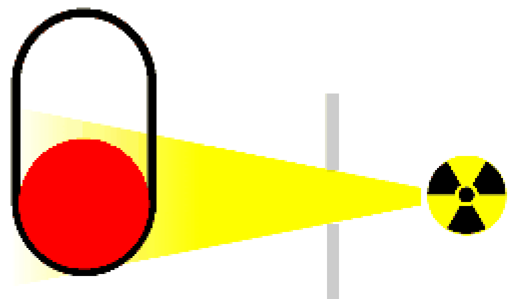
2. How to reduce **radiation-heart exposure?**

MANAGEMENT BY TRACKING OR GATING

TRACKING

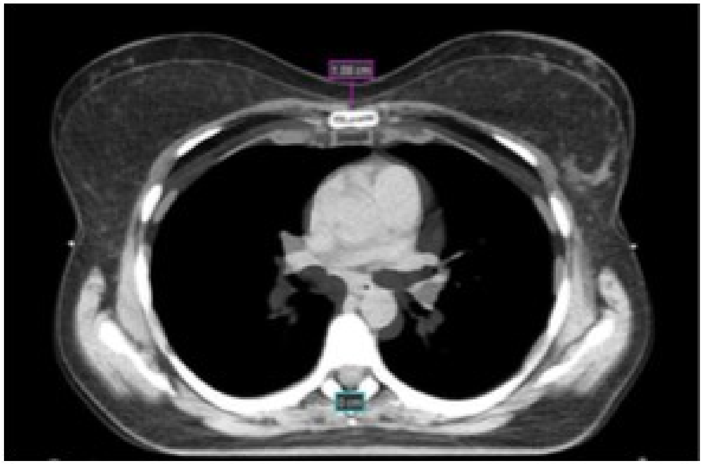


GATING



Courtesy of Prof Alongi

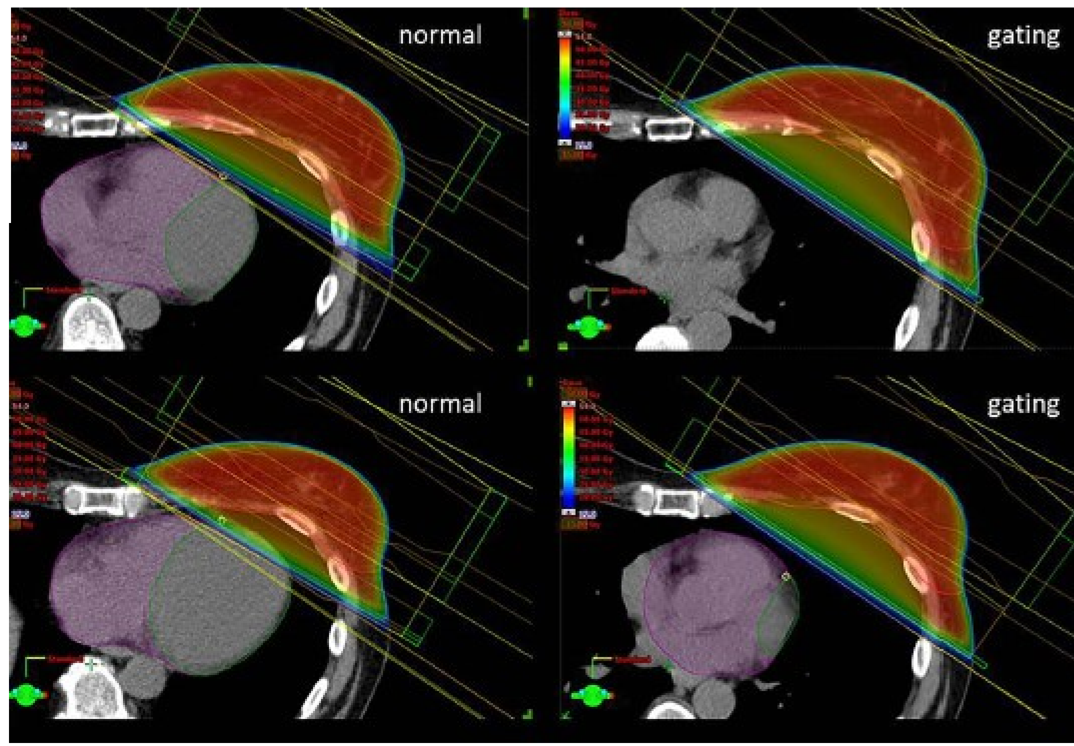
2. How to reduce **radiation-heart exposure?**
Breath-Hold Irradiation for left side BC



TC-SIM Breath-Hold

> 1 cm

TC-SIM Free-Breathing



2. How to reduce **radiation-heart exposure?**
Breath-Hold Irradiation for left side BC

IRCCS, Sacro Cuore Don Calabria Experience

Dosimetric parameters for Organs at Risk					
Heart					
	V(cm^3)	**D2%**	**DMEAN**	**V5GY**	
FB	500 (373-724)	**5,3 (2,2-25,2)**	**1,1 (0,5-2,8)**	**2,4 (0,0-9,7)**	
BH	503 (338-725)	**2,4 (1,6-5,4)**	**0,8 (0,4-1,5)**	**0 (0-2,3)**	
p-value	0,1082	**<0,0001**	**<0,0001**	**<0,0001**	
Left lung					
	V(cm^3)	D2%	DMEAN	V20GY	V5GY
FB	1340 (924-1693)	38,4 (19,7-47,7)	4,6 (2,7-7,0)	6 (2,0-11,3)	18,1 (12,1-29,0)
BH	2347 (1564-3030)	42,9 (28,2-48,1)	4,4 (2,8-7,1)	6,6 (3,1-11,7)	16,3 (10,7-25,8)
p-value	<0,0001	0,0001	0,5	0,1931	0,0214

Unpublished data

Utility of Deep Inspiration Breath Hold for Left-Sided Breast Radiation Therapy in Preventing Early Cardiac Perfusion Defects

Table 4: Pre-and 6-month post-radiotherapy (RT) cardiac parameters

Cardiac parameter evaluated(n=patients)	Average (range)
Pre-chemotherapy echocardiography-based EF (n = 3)	73% (66-83)
Post-chemotherapy/Pre-RT echocardiography-based EF (n=18)	62% (57-68)
Pre-RT wall motion score * (n=20)	0
Pre-RT perfusion SPECT summed-rest score (n=20)	0
Post-RT echocardiography-based EF (n=18)	63% (53-85)
Post-RT wall motion score *	0
Post-RT perfusion SPECT summed-rest score (n=20)	0

- EF – Ejection fraction
- Wall Motion Score, via cardiac SPECT
- Echocardiography was not required as part of the study, but was often obtained as part of the patient's regular medical care.

Zagar, et al. International Journal of Radiation Oncology*Biology*Physics, In press

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ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. e239–e246, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2011.03.058

BIOLOGY CONTRIBUTION

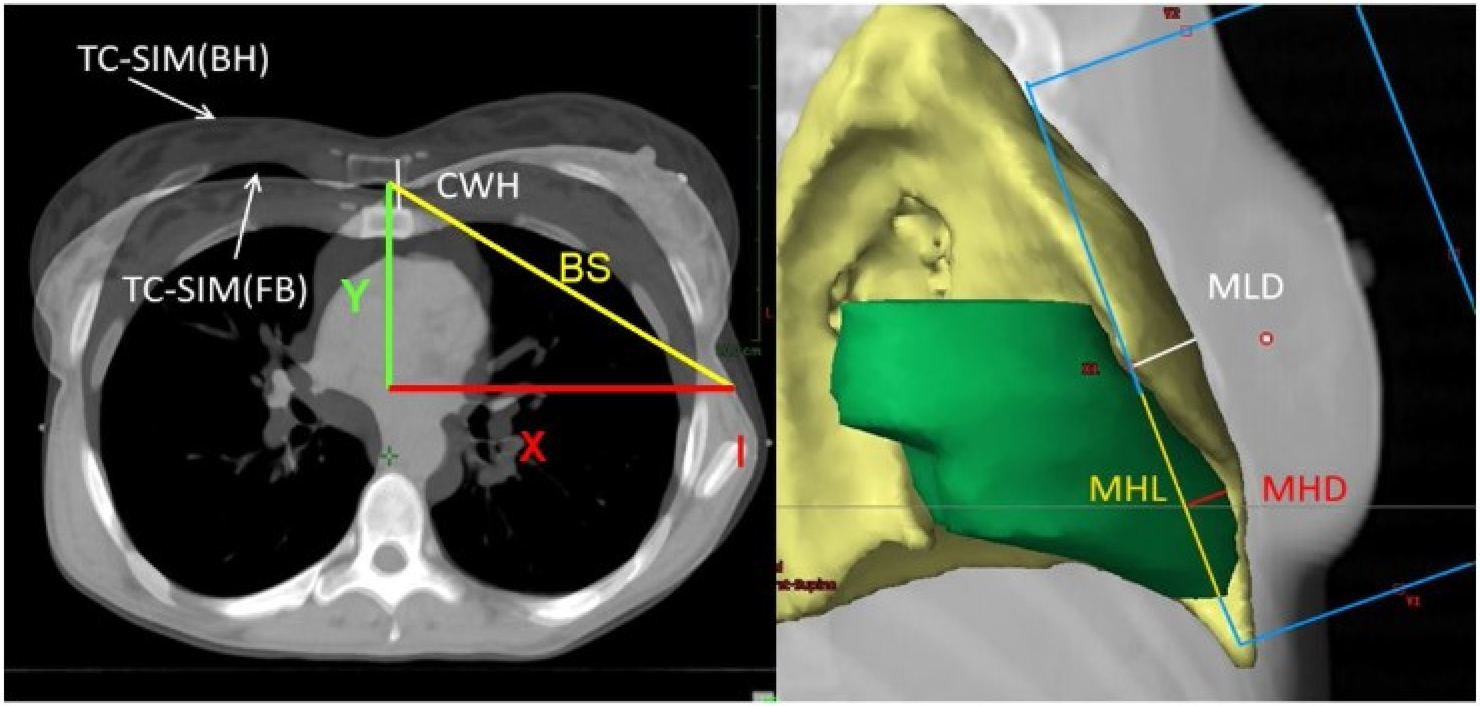
N-TERMINAL PRO-B–TYPE NATRIURETIC PEPTIDE PLASMA LEVELS AS A POTENTIAL BIOMARKER FOR CARDIAC DAMAGE AFTER RADIOTHERAPY IN PATIENTS WITH LEFT-SIDED BREAST CANCER

Maria P. D'Errico, M.Sc.,* Luca Grimaldi, M.P.,† Maria F. Petruzzelli, M.D.,‡ Emilio A. L. Gianicolo, M.S.,§ Francesco Tramacere, M.D.,‡ Antonio Monetti, M.Sc.,* Roberto Placella, M.Sc.,* Giorgio Pili, M.P.,† Maria Grazia Andreassi, M.Sc., Ph.D.,§ Rosa Sicari, M.D., Ph.D.,§ Eugenio Picano, M.D., Ph.D.,§ and Maurizio Portaluri, M.D.‡§

Departments of *Laboratory Medicine, †Medical Physics, and ‡Radiation Oncology, "A. Perrino" Hospital, Brindisi, Italy; and §Clinical Physiology Institute, National Research Council (IFC-CNR), Pisa-Lecce, Italy

Conclusions: Patients with left-sided breast cancer show higher values of NT-pro BNP after RT when compared with non–RT-treated matched patients, increasing in correlation with high doses in small volumes of heart and ventricle. The findings of this study show that the most important parameters are not the mean doses but instead the small percentage of organ volumes (heart or ventricle) receiving high dose levels, supporting the notion that the heart behaves as a serial organ. © 2012 Elsevier Inc.

3. How to predict **radiation-associated heart damage?**



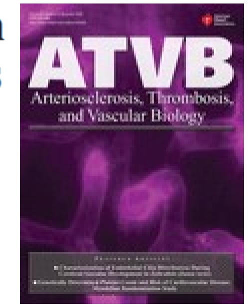
The measurements of CWH, BS, X, Y were performed in the central slice of CT_FB

The measurements of MHL and MHD and MLD were performed with respect to the posterior edge of the tangential medial field (BEV).

Courtesy of S. Naccarato. Unpublished data

Association of Plasma Ceramides With Myocardial Perfusion in Patients With Coronary Artery Disease Undergoing Stress Myocardial Perfusion Scintigraphy

Alessandro Mantovani, Stefano Bonapace, Gianluigi Lunardi, Matteo Salgarello, Clementina Dugo, Stefania Gori, Enrico Barbieri, Giuseppe Verlato, Reijo Laaksonen, Christopher D. Byrne, Giovanni Targher



Arterioscler Thromb Vasc Biol. 2018 Dec;38(12):2854-2861

Diabetes & Metabolism 44 (2018) 473–481

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Original article

Association between decreasing estimated glomerular filtration rate and risk of cardiac conduction defects in patients with type 2 diabetes

A. Mantovani [a], R. Rigolon [a], T. Turino [a], I. Pichiri [a], A. Falceri [a], A. Rossi [b], P.L. Temporelli [c], S. Bonapace [d], G. Lippi [e], G. Zoppini [a], E. Bonora [a], C.D. Byrne [f,g], G. Targher [a,*]

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CONCLUSION

In the Modern Radiation Therapy the dose reduction of heart exposure should represent a primary objective to guarantee long-term heart health

This last point is high relevant for young patients potentially long-survivors

Future predictive biomarkers could help radiation oncologists to adapt the treatment planning based on the hearth damage risk

THANK YOU FOR THE ATTENTION…