WORKSHOP

Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

Marina Guenzi

Genova

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

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.

2168 women
RT fra il 1958 e il 2001

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

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.

Exposure of the heart to ionizing **radiation during RT** for breast cancer **increases** the subsequent rate of **ischemic heart disease.**

The increase is **proportional to the mean dose** to the heart, begins within a **few years after exposure**, and continues **for at least 20 years**.

Women with **preexisting cardiac risk factors** have greater absolute increases in risk from radiotherapy than other women.

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

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.

ASTRO Talking Points

A study from Europe on breast cancer and cardiac risk associated with radiation therapy, "Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer," was published today in *The New England Journal of Medicine* (www.nejm.org). This study has been receiving a lot of news media coverage, including articles in *The New York Times*, *The Boston Globe*, *The Wall Street Journal*, *The Los Angeles Times*, and the *Associated Press*. ASTRO President-Elect Dr. Bruce Haffty was interviewed for the *Associated Press* story.

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

ASTRO Talking Points

1. The benefits of radiation therapy outweigh the risks of cardiac toxicity in the majority of patients for whom radiation therapy is indicated. Current technologies continue to advance and provide many ways to protect the heart, particularly when treating the left breast.
2. The NEJM study is a significant retrospective look at treatment from 1958-2001, but it is an analysis of patient records and is estimating the risks of radiation exposure to the heart during this time interval when technology was not as advanced as it is today.
3. While the study indicates that there is increased cardiac risk for those patients who received radiation, it is important to keep in mind the significant advances in technology from 1958 to 2001. In addition, much has changed just since 2001. It is also important to note that even with older technologies and slightly increased risk of cardiac events, there is a substantial and significant overall survival and breast cancer mortality benefit with radiation in appropriately treated breast cancer patients.
4. As with any medical intervention there remain risks and benefits to treatment. With modern technology, the risk of cardiac exposure can be minimized to levels far below those achieved in previous decades. It has clearly been shown that in patients treated by lumpectomy as well as in patients treated by mastectomy for whom radiation is indicated, the benefits of radiation, in terms of overall survival and breast cancer mortality, far exceed the potential risks.

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra volume cardiaco-dose
- Altri fattori
- Ipofrazionamento
- Entità del rischio
- Confronto vantaggi della RT/rischio

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra volume cardiaco-dose
- Altri fattori
- Ipofrazionamento
- Entita del rischio
- Confronto vantaggi della RT/rischio

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

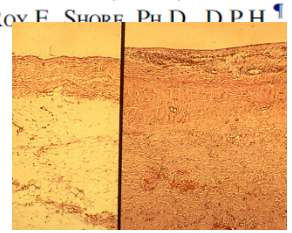
CARDIOTOSSICITA'

2010

TICAL REVIEW

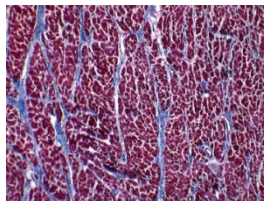
RADIATION-RELATED HEART DISEASE: CURRENT KNOWLEDGE AND FUTURE PROSPECTS

SARAH C. DARBY, PH.D.,* DAVID J. CUTTER, F.R.C.R.,* MARJAN BOERMA, PH.D.,†
LOUIS S. CONSTINE, M.D.,‡ LUIS F. FAJARDO, M.D.,§ KAZUNORI KODAMA, M.D.,¶
KIYOHIKO MABUCHI, M.D.,** LAWRENCE B. MARKS, M.D.,†† FRED A. METTLER, M.D.,‡‡
LORI J. PIERCE, M.D.,§§ KLAUS R. TROTT, M.D.,¶¶ EDWARD T. H. YEH, M.D.,***
AND ROY E. SHORE, PH.D., D.P.H.¶



ELSEVIER

Pericarditis, pericardial fibrosis,



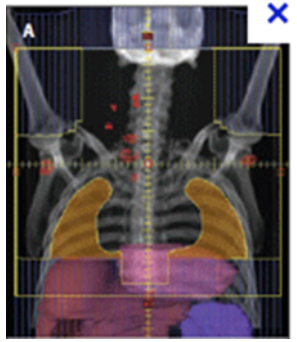
diffuse **Myocardial fibrosis,**

Conduction system,→ arrhythmias and conduction blocks

Autonomic nervous system dysfunction → persistent nonvariable tachycardia

Valvular disease

>30 Gy



WORKSHOP
Tossicità nel management del carcinoma mammario in stadio inizia

CARDIOTOSSICITA'

CRITICAL REVIEW

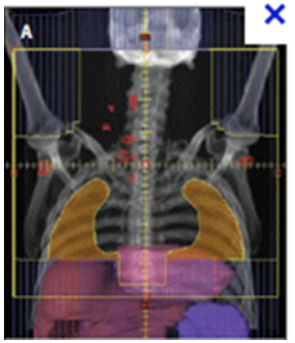
RADIATION-RELATED HEART DISEASE: CURRENT KNOWLEDGE AND FUTURE PROSPECTS

SARAH C. DARBY, PH.D.,* DAVID J. CUTTER, F.R.C.R.,* MARJAN BOERMA, PH.D.,† LOUIS S. CONSTINE, M.D.,‡ LUIS F. FAJARDO, M.D.,§ KAZUNORI KODAMA, M.D.,¶ KIYOHIKO MABUCHI, M.D.,** LAWRENCE B. MARKS, M.D.,†† FRED A. METTLER, M.D.,‡‡ LORI J. PIERCE, M.D.,§§ KLAUS R. TROTT, M.D.,¶¶ EDWARD T. H. YEH, M.D.,*** AND ROY E. SHORE, PH.D., D.P.H.¶

Conduction system, a variety of arrhythmias and conduction blocks have been observed, but these are rarely clinically serious.

Autonomic nervous system dysfunction with a persistent nonvariable tachycardia has also been described

Valvular disease (evidence not strong) related to mediastinal radiation doses of >30 Gy (**lymphoma**) younger age at irradiation, with a latency of >10 years for symptomatic and longer (median, 22 years) for symptomatic disease



WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

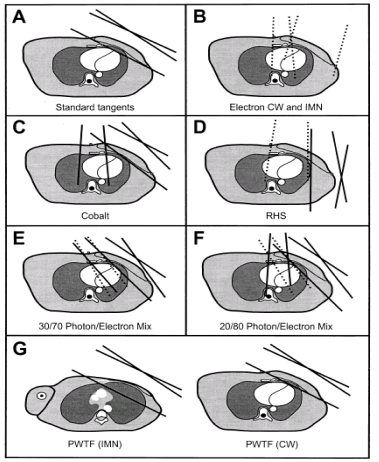


Fig. 1. Diagrammatic presentation of RT techniques.

For **breast cancer** patients, data are conflicting regarding the association of RT with **valvular dysfunction**

the risk of valvular dysfunction was higher in the group receiving IMN RT vs. the group with no RT (HR = 3.17)

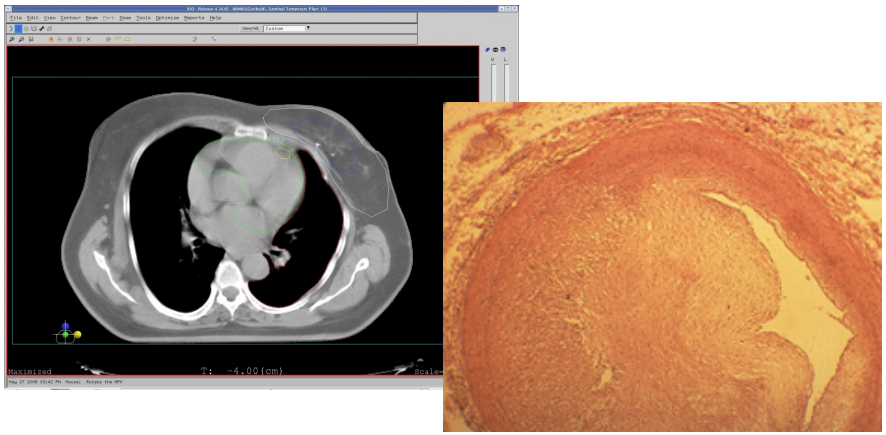
Hooning MJ, 2007

but this was not demonstrated in a smaller study

Harris EE, JCO 2006

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'



The predominant clinical manifestation today is **coronary artery disease**, but the **frequency is unknown**, as it does not differ clinically from that from other causes, and many radiation related cases may not be recognized as such.

is usually not detected until **at least 10 years** after exposure.....

the magnitude of **the risk with modern RT techniques is not yet well defined.**

S Darby, 2010

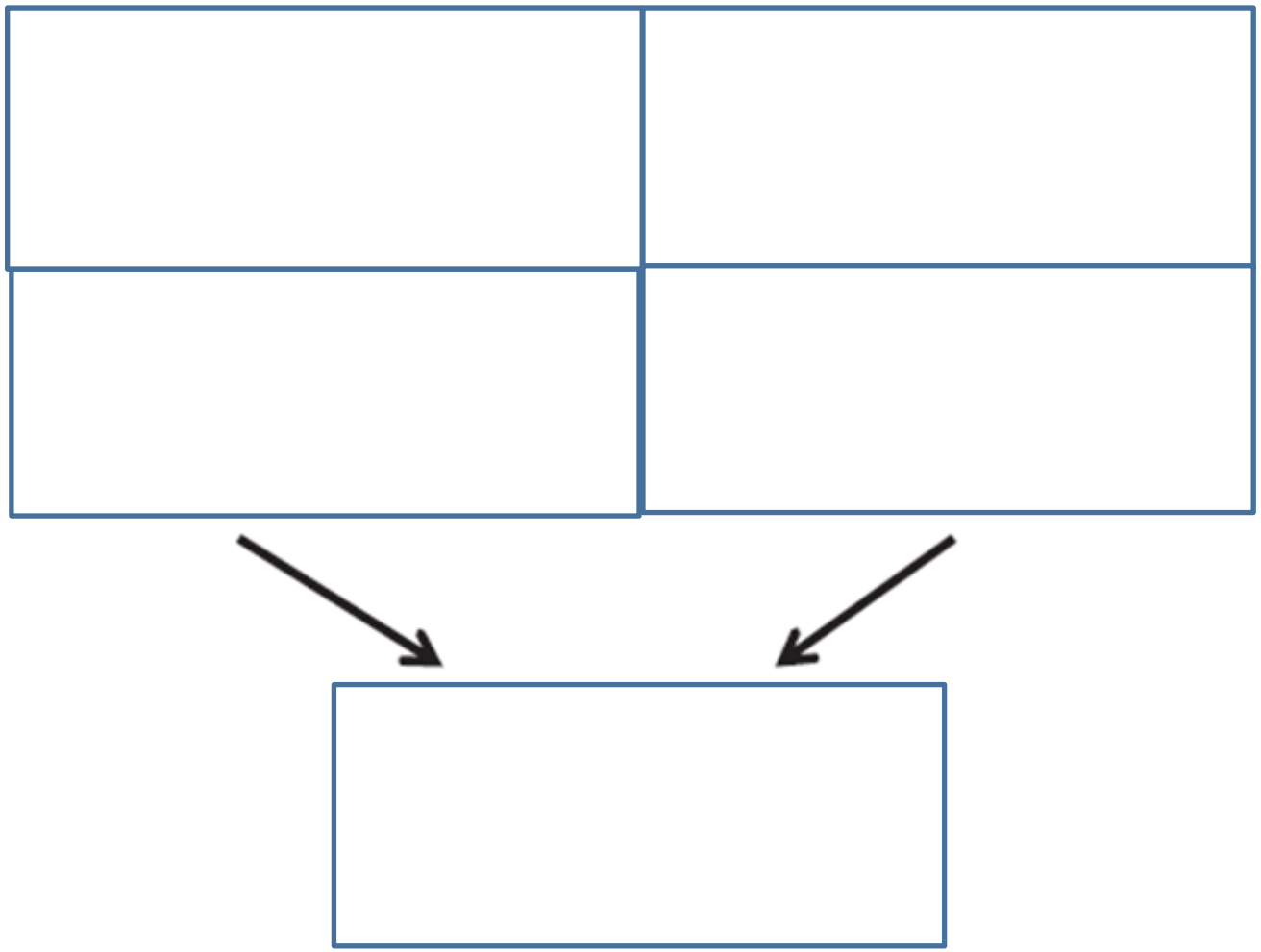
WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra volume cardiaco-dose
- Altri fattori
- Ipofrazionamento
- Entita del rischio
- Confronto vantaggi della RT/rischio

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'



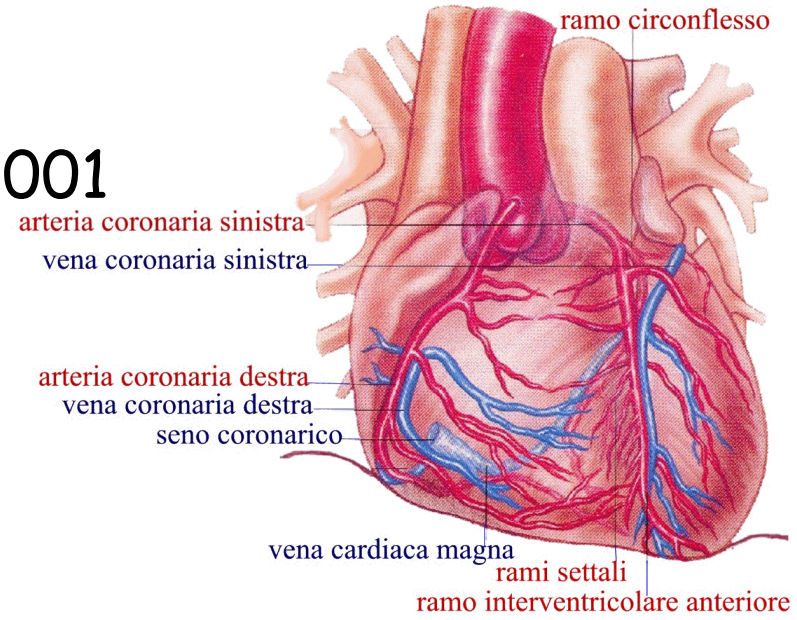
Darby S, 2010

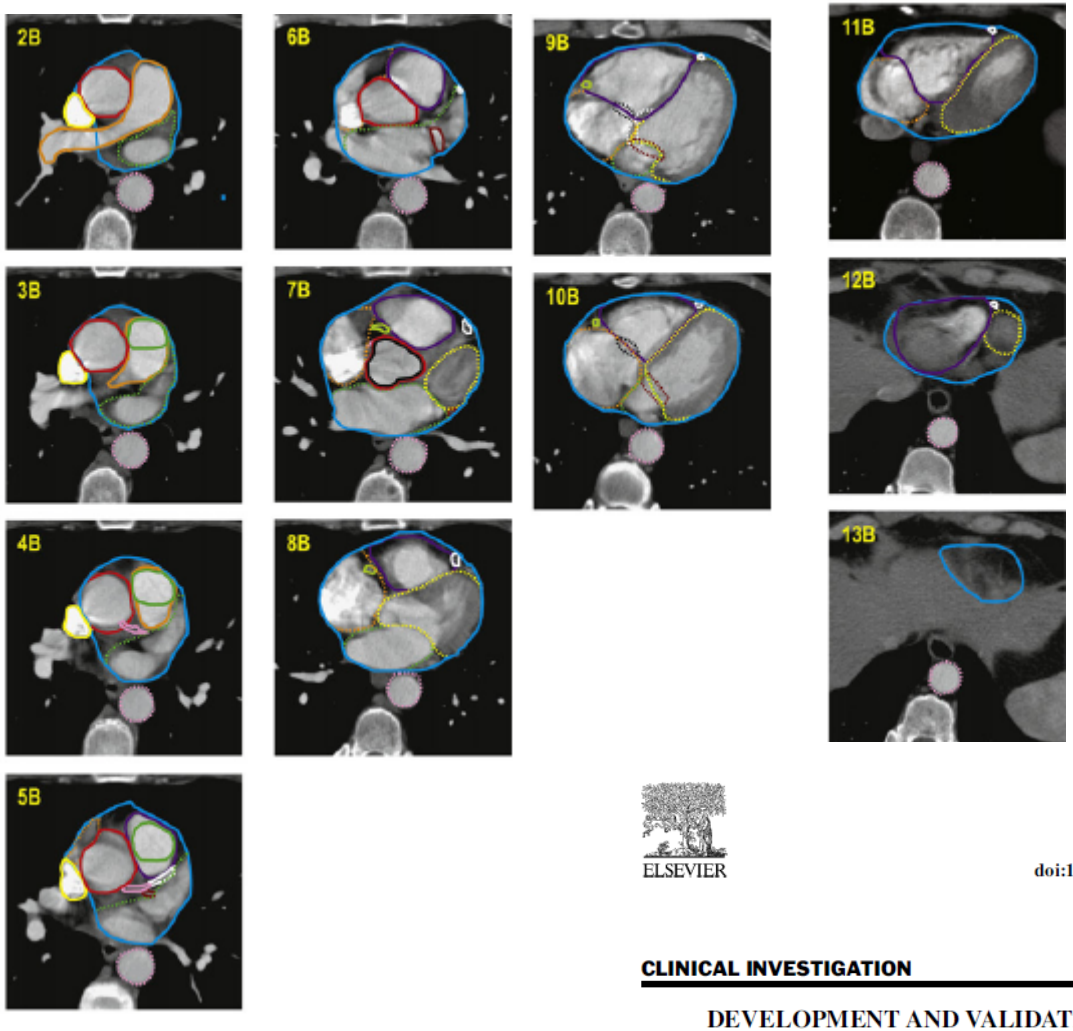
WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

In breast cancer patients, the most commonly affected vessel is the **left anterior descendent coronary artery**, usually encompassed by the highest dose volume, both in post-mastectomy and breast-conserving treatment setting.

Gagliardi G, Semin Radiat Oncol 2001
Fuller SA, 1992
Gyenes G, 1997





Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 10–18, 2011

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2009.10.058

CLINICAL INVESTIGATION **Breast**

DEVELOPMENT AND VALIDATION OF A HEART ATLAS TO STUDY CARDIAC EXPOSURE TO RADIATION FOLLOWING TREATMENT FOR BREAST CANCER

Mary Feng, M.D.,* Jean M. Moran, Ph.D.,* Todd Koelling, M.D.,† Aamer Chughtai, M.D.,‡
June L. Chan, M.D.,* Laura Freedman, M.D.,* James A. Hayman, M.D.,*
Reshma Jagsi, M.D., D. Phil.,* Shruti Jolly, M.D.,* Janice Larouere, M.D.,*
Julie Soriano, M.D.,* Robin Marsh, C.M.D.,* and Lori J. Pierce, M.D.*

Department of *Radiation Oncology; Internal Medicine, Division of †Cardiology and; ‡Radiology, University of Michigan Medical Center, Ann Arbor, Michigan

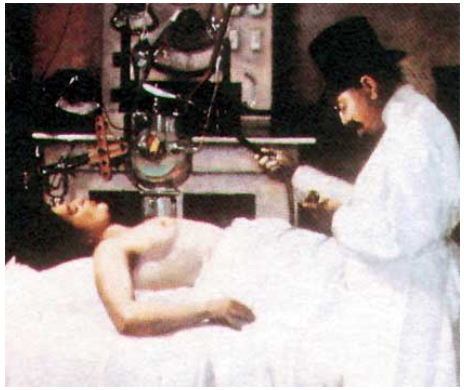
WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra volume cardiaco irradiato-dose somministrata
- Altri fattori
- Ipofrazionamento
- Entita del rischio
- Confronto vantaggi della RT/rischio

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'



Aspects of the radiotherapy techniques used in the earlier trials that contributed to the increased cardiac mortality included field placement near the heart, orthovoltage radiation that delivered high doses to the anterior part of the heart, large daily fractions, and high total doses.

Cancer and the Heart

Risks of Heart Disease after Radiotherapy

David J. Cutter, MB, BChir
Sarah C. Darby, PhD
Syed W. Yusuf, MD

Presented at the First International Conference on Cancer and the Heart; from The University of Texas MD Anderson Cancer Center and the Texas Heart Institute at St. Luke's Episcopal Hospital; Houston, 3–4 November 2010.

The **critical dose** and **volume** relationships for individual cardiac structures, and for individual cardiovascular endpoints, **are not known** with any accuracy.

For example, it is not known whether it might be advantageous to deliver a **high dose to a small volume** of the heart or a **smaller dose to a larger volume** of the heart

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

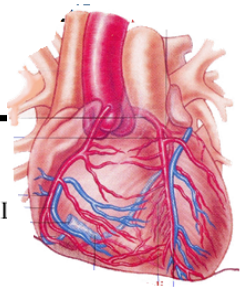
CARDIOTOSSICITA'

SEVIER

2010

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S77–S85, 2010

0360-3016/10/$–see front matter
doi:10.1016/j.ijrobp.2009.04.093



JANTEC: ORGAN SPECIFIC PAPER

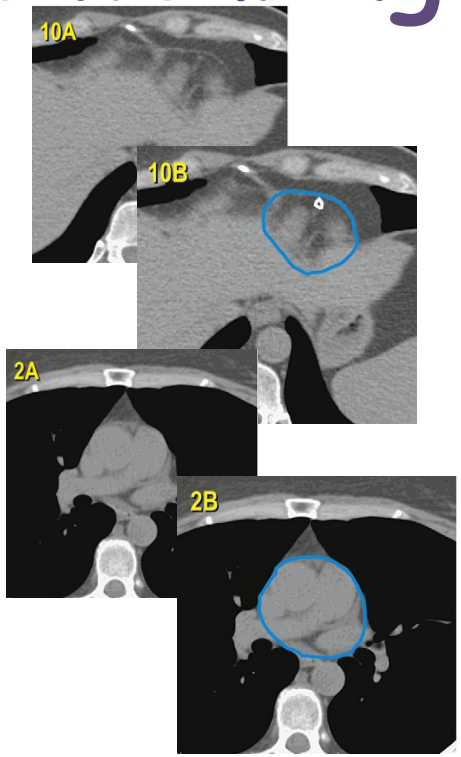
RADIATION DOSE–VOLUME EFFECTS IN THE HEART

GIOVANNA GAGLIARDI, PH.D.,* LOUIS S. CONSTINE, M.D.,† VITALI MOISEENKO, PH.I
CANDACE CORREA, M.D.,‡ LORI J. PIERCE, M.D.,‡ AARON M. ALLEN, M.D.,‖
AND LAWRENCE B. MARKS, M.D.¶

CHALLENGES IN DEFINING VOLUMES… Contouring

- structural definition through the current devices used in treatment planning (computed tomography) is imprecise

- The heart border may be difficult to differentiate from liver and diaphragm, but the segmenting of the superior border with the large vessels can be more challenging.



CARDIOTOSSICITA'

- Newer imaging tools, such as **magnetic resonance** imaging, may be able to better identify cardiac subregions, but their **application to RT planning is still limited**

- The **heart moves** with the respiratory and cardiac cycles: the degree of motion, mainly in the superior-inferior direction, **is modest with free breathing**

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

ATLANTI !!!

CARDIOTOSSICITA'

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 10–18, 2011

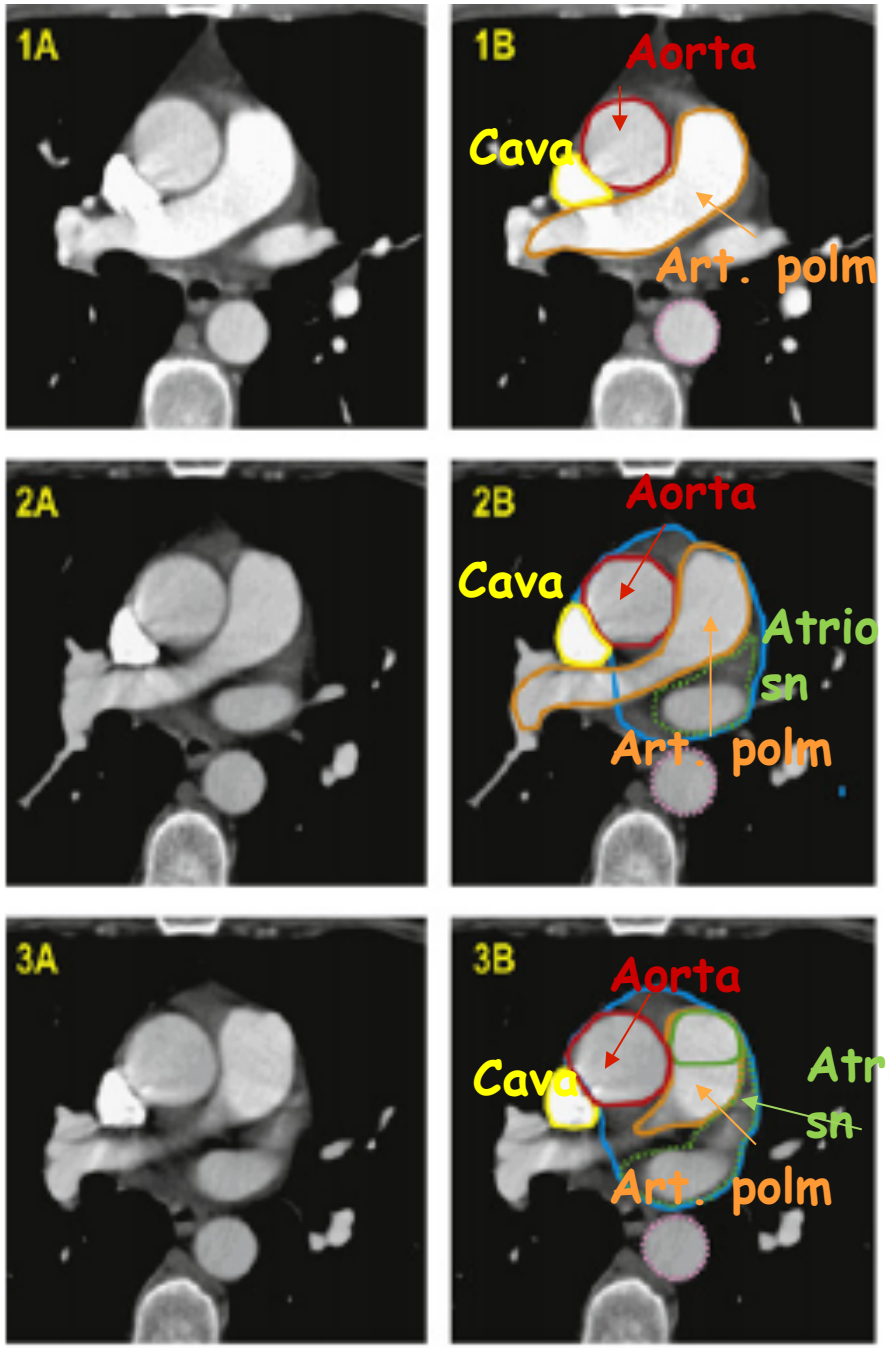
0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2009.10.058

CLINICAL INVESTIGATION **Breast**

DEVELOPMENT AND VALIDATION OF A HEART ATLAS TO STUDY CARDIAC EXPOSURE TO RADIATION FOLLOWING TREATMENT FOR BREAST CANCER

MARY FENG, M.D.,* JEAN M. MORAN, PH.D.,* TODD KOELLING, M.D.,† AAMER CHUGHTAI, M.D.,‡
JUNE L. CHAN, M.D.,* LAURA FREEDMAN, M.D.,* JAMES A. HAYMAN, M.D.,*
RESHMA JAGSI, M.D., D. PHIL.,* SHRUTI JOLLY, M.D.,* JANICE LAROUERE, M.D.,*
JULIE SORIANO, M.D.,* ROBIN MARSH, C.M.D.,* AND LORI J. PIERCE, M.D.*



WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

Superiorly, the WH starts just inferior to the left pulmonary artery.

For simplification, a round structure to include the great vessels as well can be contoured.

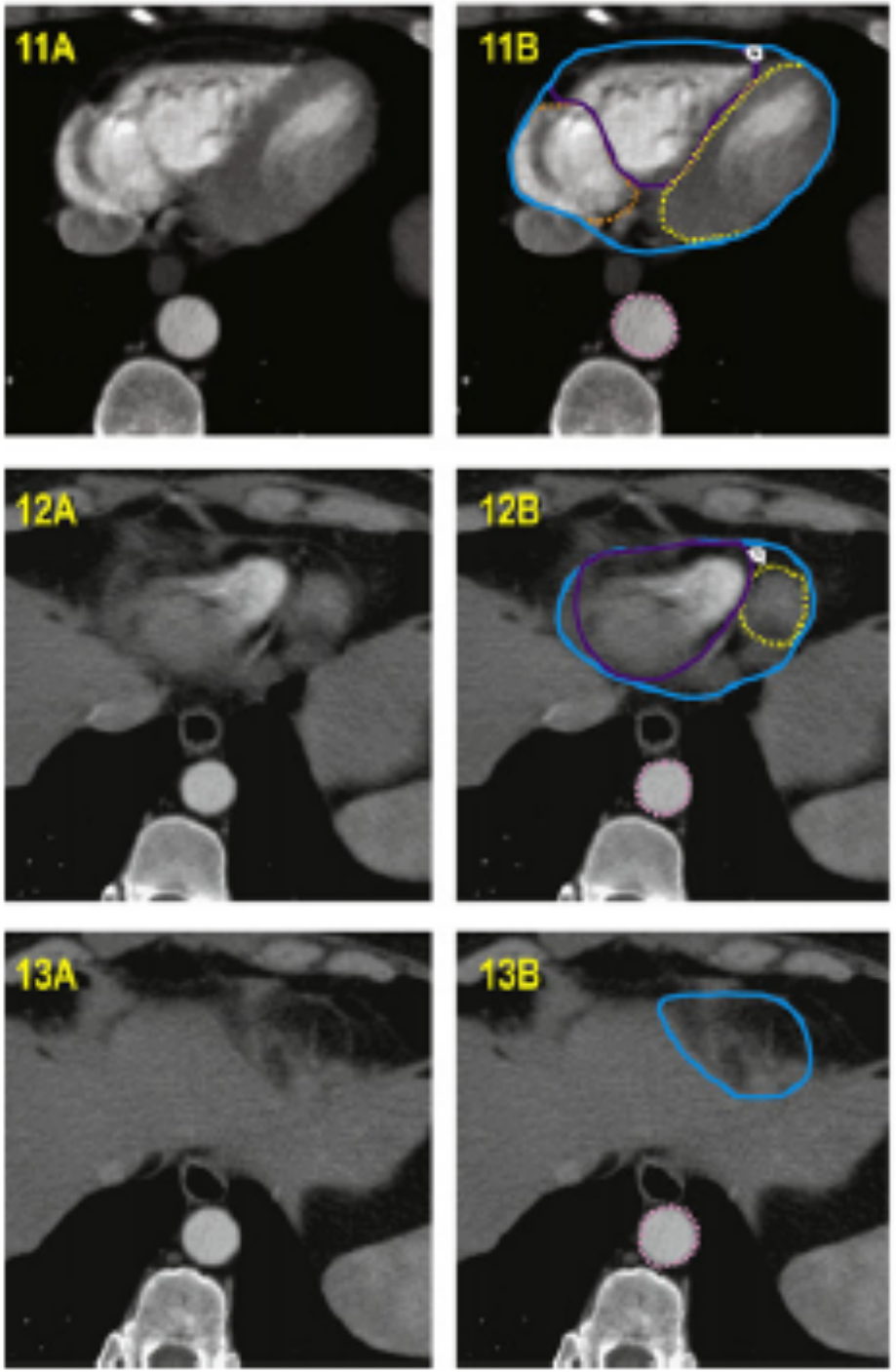
Feng M, IJROBP 2011

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

Since **cardiac vessels run in the fatty tissue within the pericardium**, they should be included in the contours, even if there is no heart muscle visible in that area

M. Feng 2011



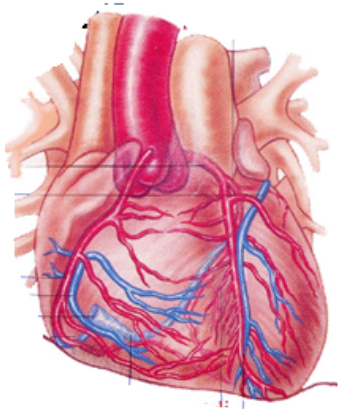
WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra volume cardiaco irradiato-dose somministrata
- Altri fattori
- Ipofrazionamento
- Entita del rischio
- Confronto vantaggi della RT/rischio

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'



Rates of major **coronary events** increased linearly with the **mean dose to the heart** by 7.4% per gray, with **no apparent threshold.**

S. Darby, 2013

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

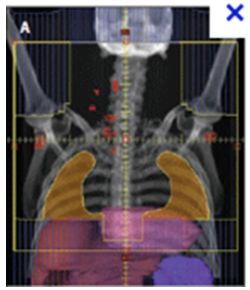
WAS

There ~~is~~ a **general view** that the **avoidance** of cardiac **doses of >30 Gy** will eliminate any **significant risk of late effects,**

but

evidence for **increased risks** from **lower doses** appears to contradict this.

Cutter DJ, 2010



WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

limitare la **V_{25} a meno del 10%** per consentire un **rischio di mortalità** a 15 anni **inferiore all' 1%**
Gagliardi G Lax I, Br J Radiol **1996**

limitare la **V30 <20 cm3**, la V40 < 10 cm3 ,la V50 < 2 cm3 per contenere il **rischio di mortalità radioindotta livelli inferiori all' 1%**
Pili G.Int J Radiat Oncol Biol Phys **2011**

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

OGGI…

CARDIOTOSSICITA'

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

Radiotherapy regimens for breast cancer have changed and the **doses** of radiation to which the heart is exposed **are now generally lower**.

AND…….

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

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

…in most women the heart still receives doses of 1 to 5 Gy .

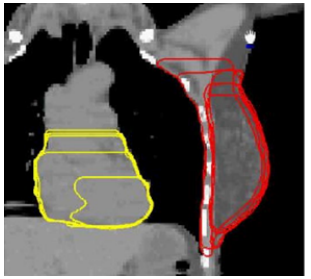
Several studies have suggested that exposures at this level can cause ischemic heart disease.

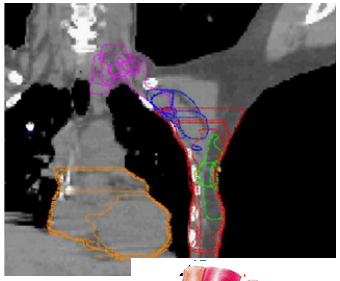
Carr ZA Coronary heart disease after radiotherapy for peptic ulcer disease. Int J Radiat Oncol Biol Phys 2005

Shimizu Y Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. BMJ 2010

Azizova TV, Cardiovascular diseases in the cohort of workers first employed at Mayak PA in 1948–1958. Radiat Res 2010;

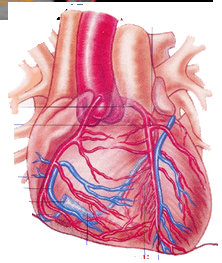
WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale





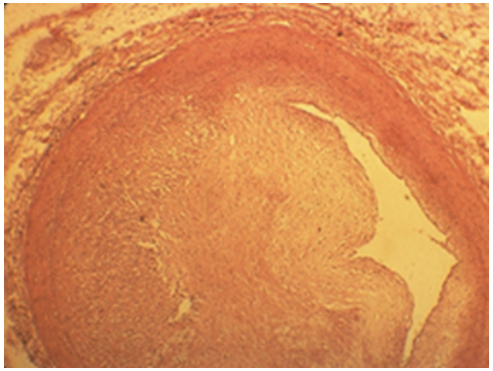
CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra ~~volume~~ cardiaco irradiato-dose somministrata a cuore



- Altri fattori
- Ipofrazionamento
- Entita del rischio
- Confronto vantaggi della RT/rischio

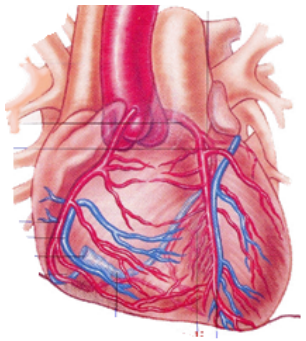
  - **doses of >30 Gy**
  - **V_{25} a meno del 10%**
  - **all'apice cardiaco <12 Gy**
  - **V30 < 20 cm3**

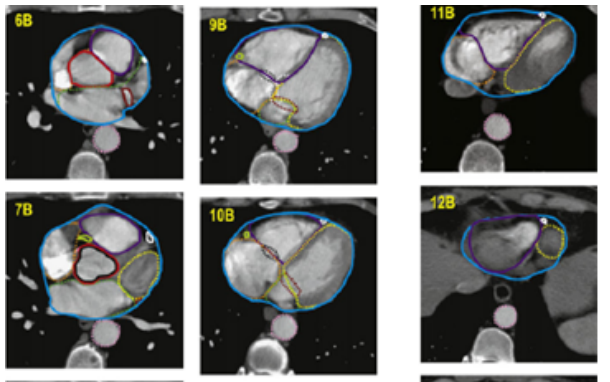


The NEW ENGLAND JOURNAL of MEDICINE

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

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





- Coronary-ischemic events are a major concern, several investigators have calculated **doses to coronary arteries**

Gagliardi G, Quantec 2010

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

Acta Oncologica, 2013; 52: 703–710

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

It has high priority to spare the OAR as much as possible from radiation

The priorities are:

CTV-boost > LADCA > heart > lung > CTV-breast/chest wall > CTV-periclavicularis > CTV-IMN > contralateral breast.

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

Acta Oncologica, 2013; 52: 703–710

CARDIOTOSSICITA'

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	$V_{20Gy} = 10\%$, $V_{40Gy} = 5\%$

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra **volume** cardiaco irradiato-**dose** somministrata
- Altri fattori..correlati alla paziente
- Ipofrazionamento
- Entita del rischio
- Confronto vantaggi della RT/rischio

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

a history of ischemic heart disease

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

the overall rate ratio for a major coronary event among women with a history of ischemic heart disease as compared with women with no such history was 6.67

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

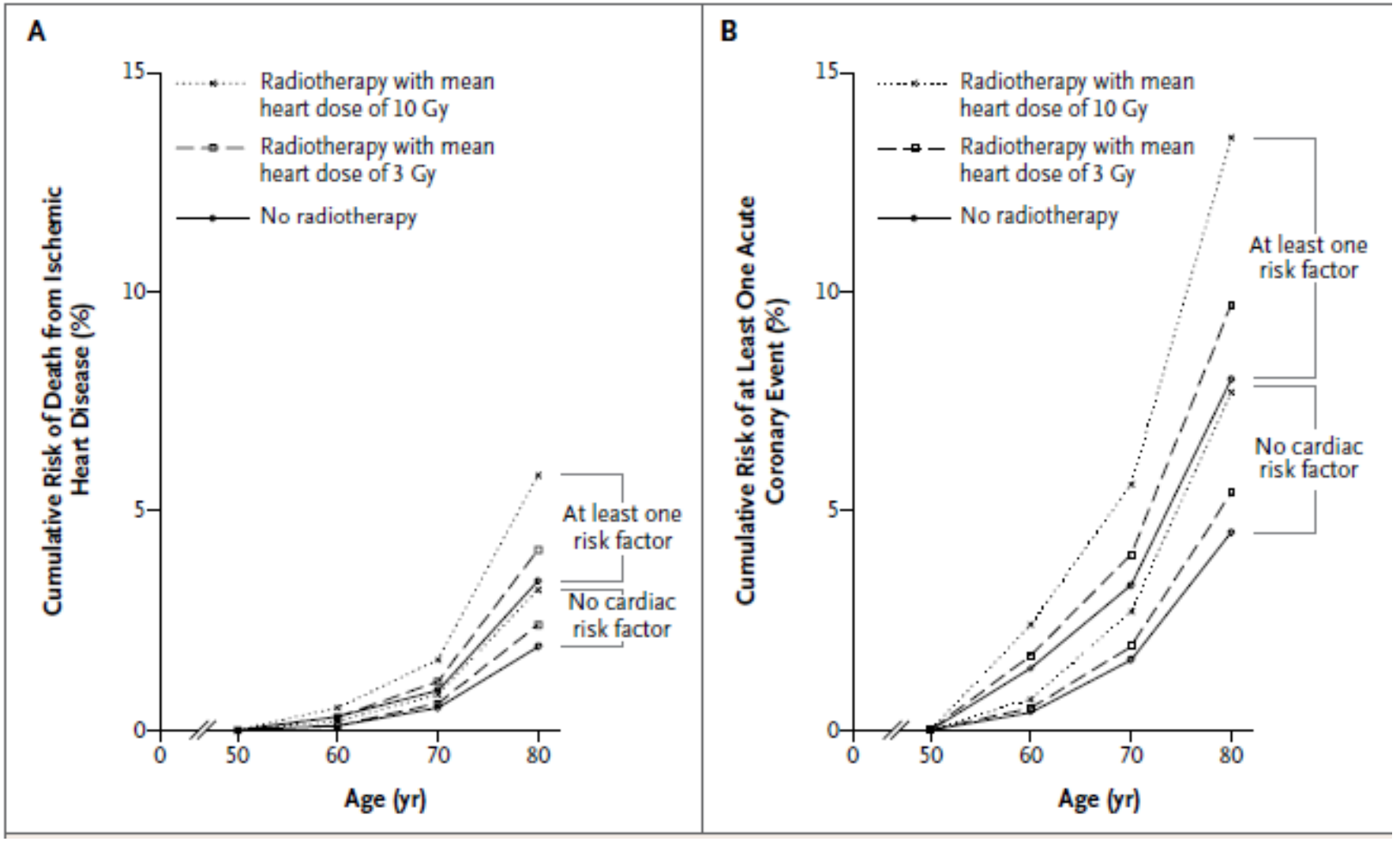
Rates of major coronary events were also elevated among women with

history of other **circulatory diseases**,
diabetes,
chronic obstructive **pulmonary disease**;
among women who **smoked**;
among women with a **high body-mass index**
a history of **regular analgesic use**.

The rate ratio for the presence of **one or more** of these factors but no ischemic heart disease was **1.96 overall**

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



WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra **volume** cardiaco irradiato-**dose** somministrata
- Altri fattori...correlati ai trattamenti
- Ipofrazionamento
- Entita del rischio
- Confronto vantaggi della RT/rischio

special article

Annals of Oncology
doi:10.1093/annonc/mdr304

Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

A. Goldhirsch[1,*], W. C. Wood[2], A. S. Coates[3], R. D. Gelber[4], B. Thürlimann[5], H.-J. Senn[6] & Panel members[†]

both anthracyclines and taxanes should be included in the chemotherapy regimen.

'Subtype'	Type of therapy
'Luminal A'	Endocrine therapy alone
'Luminal B (HER2 negative)'	Endocrine ± cytotoxic therapy
'Luminal B (HER2 positive)'	Cytotoxics + anti-HER2 + endocrine therapy
'HER2 positive (non luminal)'	Cytotoxics + anti-HER2
'Triple negative (ductal)'	Cytotoxics
'Special histological types'*	
A. Endocrine responsive	Endocrine therapy
B. Endocrine nonresponsive	Cytotoxics

Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed efficacy of adjuvant chemotherapy compared with no chemotherapy, superiority of anthracycline-based regimens over CMF and of taxane-containing regimens over those based on anthracycline. The relative magnitude of benefit from anthracycline or anthracycline-taxane combinations resulted in similar reductions of breast cancer mortality irrespective of age, stage, histopathological grade and ER status, although the absolute gain for a low disease burden Luminal A-type of cancer will be very small [18, 19].

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra **volume** cardiaco irradiato-**dose** somministrata
- Altri fattori
- Ipofrazionamento
- Entita del rischio
- Confronto vantaggi della RT/rischio cardiotox
- Come evitare
- conclusioni

CRITICAL REVIEW

HYPOFRACTIONATED WHOLE-BREAST RADIOTHERAPY FOR WOMEN WITH EARLY BREAST CANCER: MYTHS AND REALITIES

JOHN YARNOLD, F.R.C.R.,* SØREN M. BENTZEN, D.SC.,† CHARLOTTE COLES, PH.D.,‡

The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

*The START Trialists' Group**

The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial

*The START Trialists' Group**

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Jean-Philippe Pignol, M.D., Mark N. Levine, Jim A. Julian, Ph.D., Robert MacKenzie, M.D., Sameer Parpia, M.Sc., Wendy Shelley, M.D., Laval Grimard, M.D., Julie Bowen, M.D., Himu Lukka, Francisco Perera, M.D., Anthony Fyles, M.D., Ken Schneider, M.D., Sunil Gulavita, M.D., and Carolyn Freeman, M.D.

CLINICAL INVESTIGATION

FRACTIONATION FOR WHOLE BREAST IRRADIATION: AN AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) EVIDENCE-BASED GUIDELINE

BENJAMIN D. SMITH, M.D.,* SOREN M. BENTZEN, PH.D., D.SC.,† CANDACE R. CORREA, M.D.,‡ CAROL A. HAHN, M.D.,§ PATRICIA H. HARDENBERGH, M.D.,¶ GEOFFREY S. IBBOTT, PH.D.,‖ BERYL MCCORMICK, M.D., FACR.,# JULIE R. MCQUEEN, CHES., RHED.,** LORI J. PIERCE, M.D.,†† SIMON N. POWELL, M.D., PH.D.,# ABRAM RECHT, M.D.,§§ ALPHONSE G. TAGHIAN, M.D., PH.D.,¶¶ FRANK A. VICINI, M.D., FACR.,‖‖ JULIA R. WHITE, M.D.,## AND BRUCE G. HAFFTY, M.D.***

START A

	Fractionation schedule			Total n=2236 (%)
	50 Gy n=749	41·6 Gy n=750	39 Gy n=737	
Ischaemic heart disease*				
Reported	12 (1·6)	7 (0·9)	8 (1·1)	27 (1·2)
Confirmed† [left-sided]‡	3 (0·4) [1]	2 (0·3) [0]	5 (0·7) [4]	10 (0·4) [5]

START B

	Fractionation schedule		Total n=2215
	50 Gy n=1105	40 Gy n=1110	
Ischaemic heart disease*			
Reported	19 (1·7)	15 (1·3)	34 (1·5)
Confirmed† [left-sided]‡	12 (1·1) [4]	7 (0·6) [3]	19 (0·9) [7]

showed that the relative effects of different fractionation schedules remain unchanged over time.

START A

	Fractionation schedule			Total n=2236 (%)
	50 Gy n=749	41·6 Gy n=750	39 Gy n=737	
Ischaemic heart disease*				
Reported	12 (1·6)	7 (0·9)	8 (1·1)	27 (1·2)
Confirmed† [left-sided]‡	3 (0·4) [1]	2 (0·3) [0]	5 (0·7) [4]	10 (0·4) [5]

15–20 years of follow-up will be needed to reliably measure cardiac effects.

The short-term priority is to protect the heart from exposure to radiotherapy, regardless of radiation schedule, since there appears to be no safe lower dose limit, however fractionated

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra **volume** cardiaco irradiato-**dose** somministrata
- Altri fattori
- Ipofrazionamento
- Entità del rischio
- Confronto vantaggi della RT/rischio cardiotox

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

Nei paesi industrializzati le **malattie cardiovascolari** sono **la prima causa di morte** (**54% dei decessi**) e di disabilità della **donna nella terza età**

European Heart Network. European cardiovascular disease statistics 2008. http:// www.ehnheart.org/component/ downloads/

BMC Cancer 2007,
BMC Cancer

BioMed Central

Research article

Open Access

Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study

Rahul Roychoudhuri[1], David Robinson*[1], Venkata Putcha[1], Jack Cuzick[2], Sarah Darby[3] and Henrik Møller[1,4]

A total of **20,871 women** with breast cancer were included in the analysis, of which **51%** had left sided disease.

All cases of female breast cancer diagnosed between **1971 and 1988** and recorded on the Thames Cancer Registry database

CON QUALE TECNICA ???
E QUALE DOSE AL CUORE E ALLA CORONARIA?

BMC Cancer

BioMed Central

Research article

Open Access

Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study

Rahul Roychoudhuri[1], David Robinson*[1], Venkata Putcha[1], Jack Cuzick[2], Sarah Darby[3] and Henrik Møller[1,4]

Diagnosed between 1971 and 1988 and recorded on the Thames Cancer Registry database

A woman who had breast cancer at the age of 50

A woman who had breast cancer at the age of 50

survived to the age of 65

survived to the age of 65

22% risk of dying from cardiovascular disease in the next 20 years, up to the age of 85

30% risk of dying from cardiovascular disease in the next 20 years, up to the age of 85

BMC Cancer

BioMed Central

Research article

Open Access

Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study

Rahul Roychoudhuri[1], David Robinson*[1], Venkata Putcha[1], Jack Cuzick[2], Sarah Darby[3] and Henrik Møller[1,4]

All of the patients in our study were treated for breast cancer in the 1970s and 1980s.

During this period, techniques involving large fraction sizes, deep tangential fields or direct internal mammary fields were common.

Since then, technical improvements in radiotherapy delivery have resulted in lower cardiac dosage

BJC 2013 SHORT COMMUNICATION

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

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*

Mortality ratios, by laterality of breast cancer….for **558 871 women** recorded with breast cancer during **1973–2008** in the **SEER** and followed until 01 January 2009.

Calendar year of diagnosis	Women Left / right	Person-years Left / right	Heart disease deaths Left / right
	Radiotherapy recorded		
1973–82	7109 / 6615	86 198 / 81 516	926 / 624
1983–92	14 582 / 13 945	195 017 / 187 240	844 / 783
1993–02	56 094 / 54 369	475 475 / 461 071	1160 / 1155
2003–08	52 500 / 51 762	151 899 / 150 327	187 / 181
Total: radiotherapy recorded	**130 285 / 126 691**	**908 589 / 880 154**	**3117 / 2743**
Mortality ratio	—	—	**1.08 (1.03–1.14)[a]**

BJC

SHORT COMMUNICATION

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

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

Pts treated **1973–2008**
followed until 01 January **2009**.

	Heart disease deaths Left / right	
1973–82	926 / 624	**302 morti in più SN**
1983–92	844 / 783	61 morti in più SN
1993–02	1160 / 1155	5 morti in più
2003–08	187 / 181	
Total: radiotherapy recorded	**3117 / 2743**	
Mortality ratio	**1.08 (1.03–1.14)[a]**	

FU minimo 27 anni

FU minimo 17 anni

FU minimo 7 anni

BJC 2013 SHORT COMMUNICATION

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

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*

The **eventual risks** for breast cancer patients given radiotherapy today are, as yet, **unknown**, but **will depend on the doses to the heart.**

….e alla coronaria….

BJC

SHORT COMMUNICATION

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

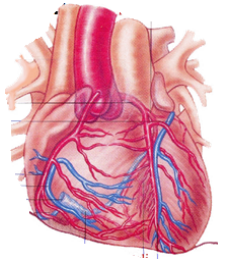
Keywords: epidemiology; breast cancer radiotherapy; radiation-related heart disease; radiation-related lung cancer; long-term effects; mortality

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

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

Today in breast cancer RT…..



The **current average mean heart dose** is likely to be around

1,45–7Gy for left-sided

Taylor et al, 2008;
Jagsi et al, 2010;
Schubert et al, 2011
Jacobson GM, 2013

1.5 Gy for right-sided

Taylor et al, 2008

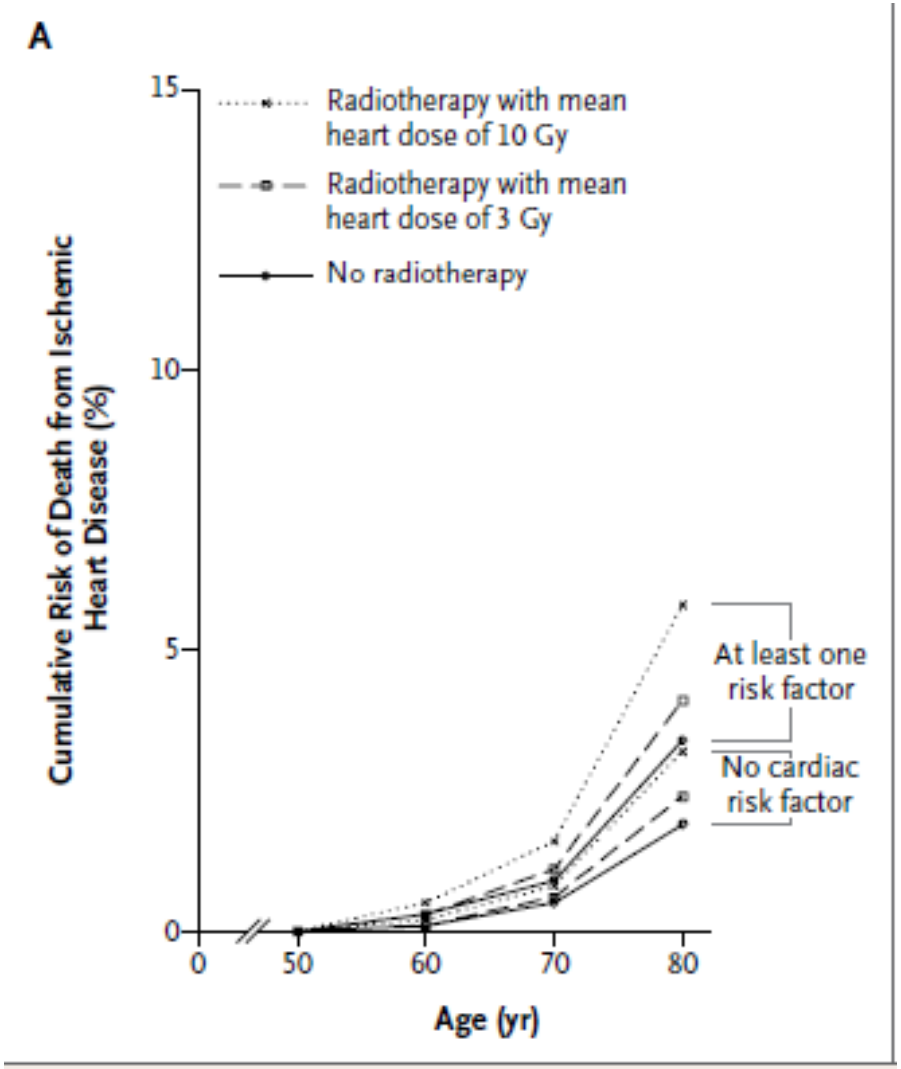
1-3 Gy

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

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



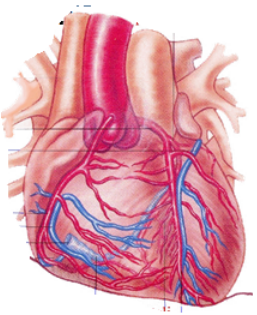
radiotherapy involving a **mean dose** of radiation to the heart of **3 Gy** in a **50-year-old woman**

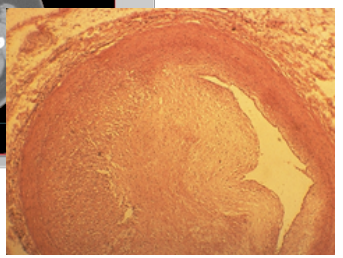
with **one or more cardiac risk factors**

would increase her **risk of death** from ischemic heart disease **before the age of 80** years **from 3.4% to 4.1**

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'





- Quali manifestazioni patologiche
- Etiopatogenesi

The predominant clinical manifestation today is **coronary artery disease**, but the frequency is unknown……

the magnitude of **the risk with modern RT techniques is not yet well defined.**

S Darby, 2010

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Eziopatogenesi
- **Quali conclusioni?**
- **Come ci dobbiamo comportare??**
- Entità del rischio
- Vantaggi della R/rischio.....

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

2013

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

Coronary artery disease after radiation therapy is a subject that is **near** and **dear** to my heart.

WORKSHOP
Tossicità nel management del
carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

2013

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

Approximately **26 years after** receiving **mantle field RT** in 1981 for Hodgkin disease, I had a **near-fatal acute myocardial infarction**

Of course, it is fair to conclude that **if I had not been cured of HD, I would not have been around to worry** about the acute myocardial infarction more than 2 dozen years later.

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

At the time I was treated it was generally **believed that RT did not cause or exacerbate Coronary Artery Disease** in HD patients.

……..

The concern for **Coronary Artery Disease** in breast cancer patients has been **slower to develop**.

……

Radiation tolerance of the coronary arteries has not been well studied beyond the observation that RT doses used for HD increase the risk of CAD.

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

Historically there have been recommendations to use the dose-volume histogram (DVH) for the heart as a whole organ.
Gagliardi G, 2010 QUANTEC

This assumed that the heart was an organ with "**parallel subunit" toxicity**, in that tolerance was acceptable if only a small volume of heart received a high RT dose as long as most of the heart received a low dose.

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

Coronary arteries are really a "**series subunit**" organ like the spinal cord
Marks LB, IJROBP 2010

Damage to any portion of a coronary artery will produce potentially **devastating toxicity** even if the rest of the artery is not irradiated.

Therefore **heart DVH** determinations are of **little usefulness** to estimate risk of CAD.
Taylor, 2008

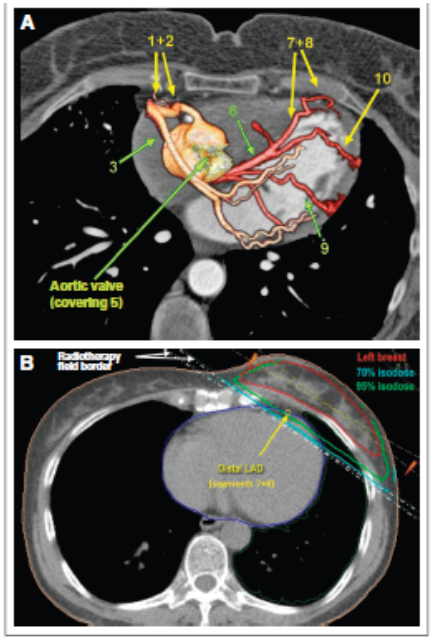


Fig 2. (A) Coronary angiogram superimposed on computed tomography (CT) of heart illustrating anatomy of coronary arteries with branches of right coronary artery (orange) and left circumflex and left anterior descending (LAD) arteries (red); numbered arrows indicate segments. (B) CT dose-planned left tangential breast irradiation showing distal LAD (yellow circle) and radiation fields.

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

Patients treated for left breast cancer with tangential RT fields may have a low mean heart dose and a very broad range of doses to the LAD branches.

CLINICAL INVESTIGATION **Breast**

CARDIAC DOSE FROM TANGENTIAL BREAST CANCER RADIOTHERAPY IN THE YEAR 2006

CAROLYN W. TAYLOR, F.R.C.R.,* JULIE M. POVALL, M.SC.,† PAUL MCGALE, PH.D.,* ANDREW NISBET, PH.D.,‡ DAVID DODWELL, M.D.,† JONATHAN T. SMITH, F.R.C.R.,† AND SARAH C. DARBY, PH.D.*

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

CLINICAL INVESTIGATION Breast

CARDIAC DOSE FROM TANGENTIAL BREAST CANCER RADIOTHERAPY IN THE YEAR 2006

CAROLYN W. TAYLOR, F.R.C.R.,* JULIE M. POVALL, M.SC.,† PAUL MCGALE, PH.D.,* ANDREW NISBET, PH.D.,‡ DAVID DODWELL, M.D.,† JONATHAN T. SMITH, F.R.C.R.,† AND SARAH C. DARBY, PH.D.*

Reduction in **mean dose** to cardiac structures from left tangential radiotherapy, **1970s–2006**

Calendar period	Heart	LAD coronary artery
Mean dose (Gy)		
1970s (Sweden) (4)	13.3	31.8
1990s (Sweden) (4)	4.7	21.9
2006 (United Kingdom)	2.3	7.6

These doses are considerably **lower** than cardiac doses from the regimens that **are now known to have caused excess cardiac mortality**, hence their risk is likely to be lower.

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

Recommendations based on my personal opinion include the following:

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

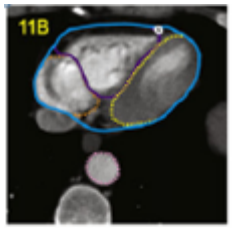
EDITORIAL

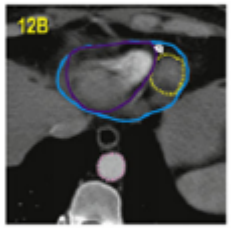
Coronary Artery Disease and Breast Radiation Therapy

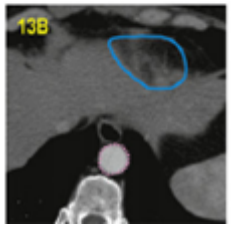
Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

- Every effort should be made to **exclude the entire cardiac silhouette** from tangential photon beam RT fields.







Computed tomography simulation is essential to design left breast cancer RT fields that maximally spare the heart.

accurato contornamento del cuore, grossi vasi con particolare attenzione alle coronaria, sulla base degli atlanti disponibili

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

- The coronary arteries should be considered a "**series**" **organ,** whereas the whole heart should be considered a "parallel" organ.

- Whole-heart DVHs are of little value in reducing the risk of CAD after chest RT.

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

- **Respiratory gating** should be further investigated as to whether it may reduce RT dose to the coronary arteries.

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

- **Selective use of internal mammary** node RT fields has reduced the frequency of Coronary Artery Disease in breast cancer patients .

Care needs to be taken to avoid irradiating the root of the aorta where the Right CA and Left Main CA originate

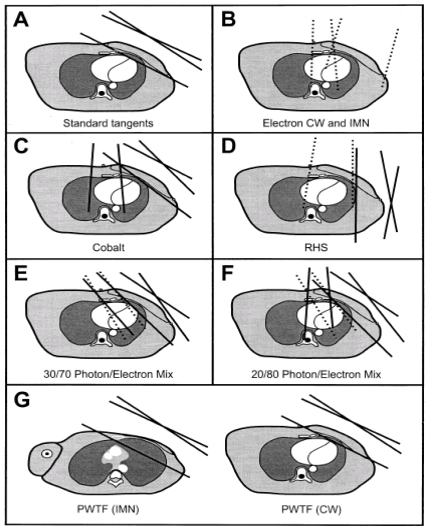
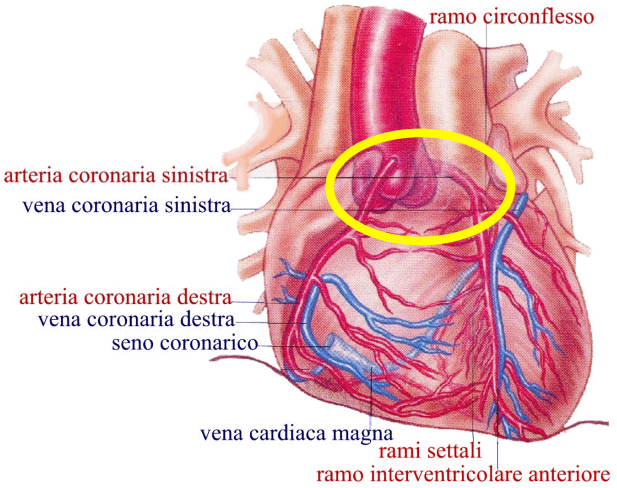


Fig. 1. Diagrammatic presentation of RT techniques.



WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

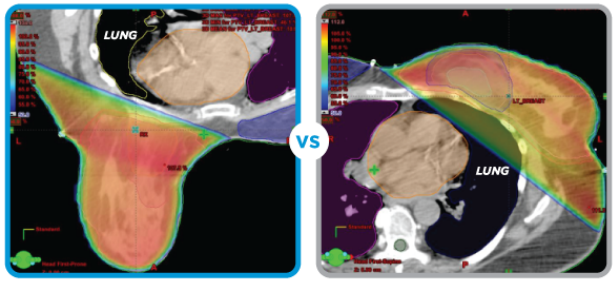
EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

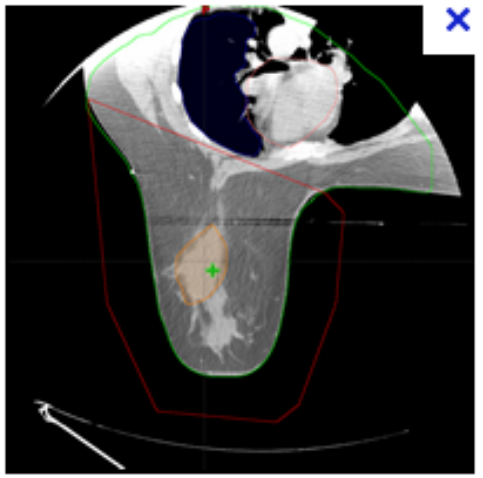
Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

- **Prone patients position** should be considered in appropriate patients.



……prone positioning was **more protective** of the heart **85%** of the time.



Supine positioning offered greater protection of the heart to about 15% of the women, usually those with very small breasts

S. Formenti JAMA, 2012

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

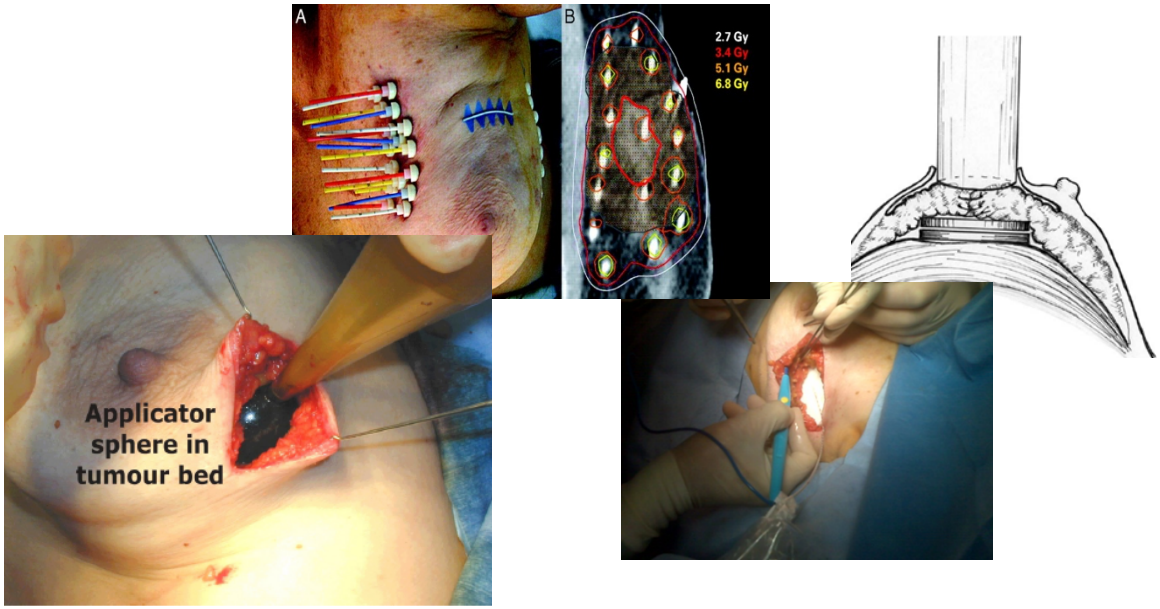
EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

- **Partial breast brachytherapy and intraoperative RT** techniques may minimize RT dose to the coronary arteries if the tumor bed does not overlay the heart.



WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

- **Intensity modulated radiation therapy**, either whole breast or partial breast, **may reduce the maximum dose to the coronary arteries.**

- However there is very **little information** concerning **maximum tolerable dose for the coronary arteries**.

WORKSHOP
Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'

EDITORIAL

Coronary Artery Disease and Breast Radiation Therapy

Richard D. Pezner, MD

Radiation Oncology Department, City of Hope Medical Center, Duarte, California

- There have been only a few studies that address whether RT acts additively or synergistically with known CAD risk factors such as **smoking, hypercholesterolemia, hypertension, and diabetes**.

- Nevertheless, **radiation oncologists should strongly encourage their patients** who have received chest RT to work with their primary care physicians **to control these recognized CAD risk factors.**

WORKSHOP

Tossicità nel management del carcinoma mammario in stadio iniziale

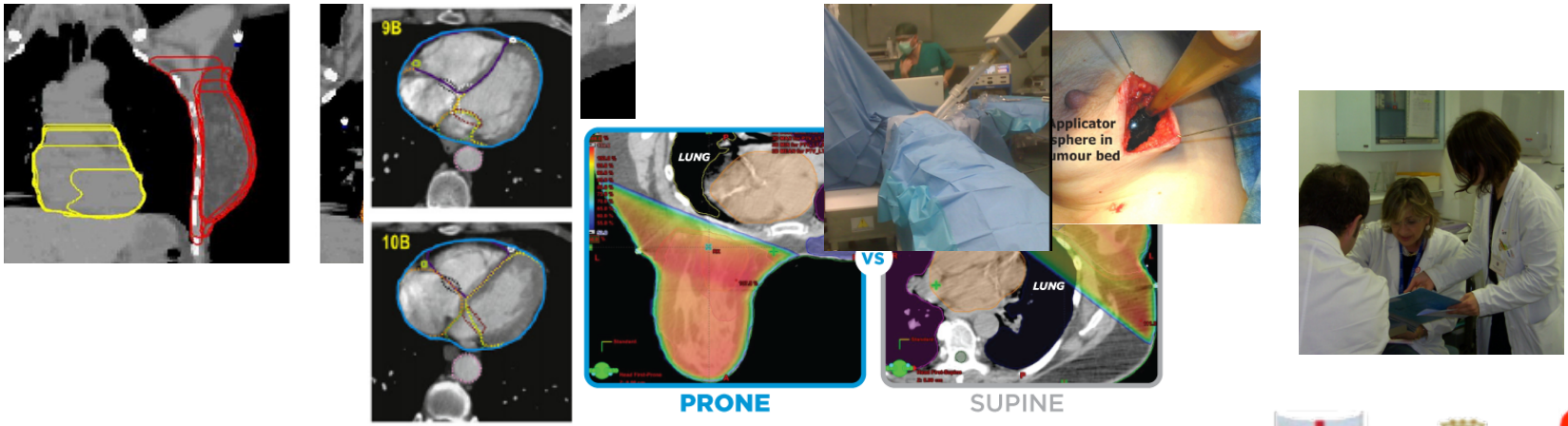
CARDIOTOSSICITA'

- Quali manifestazioni patologiche
- Etiopatogenesi
- Correlazioni fra volume cardiaco-dose
- Altri fattori
- Ipofrazionamento
- Entità del rischio
- Confronto vantaggi della RT/rischio

WORKSHOP

Tossicità nel management del carcinoma mammario in stadio iniziale

CARDIOTOSSICITA'



Marina Guenzi

Genova