Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

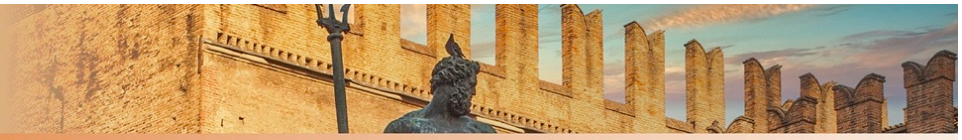
DRUG LAB n. 2

La terapia sistemica prima della radioterapia. Dalla conoscenza dei farmaci alla gestione della tossicità della radioterapia: chemioterapia

Antracicline: la cardiotossicità e la tossicità cutanea

Corrado Spatola

Associazione Italiana Radioterapia e Oncologia clinica
Società Italiana di Radiobiologia



DICHIARAZIONE CONFLITTO DI INTERESSI

Relatore: CORRADO SPATOLA

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Consulenza ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Partecipazione ad Advisory Board (NIENTE DA DICHIARARE)
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)

Farmaci cardiotossici

Supplement submission
OPEN
FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

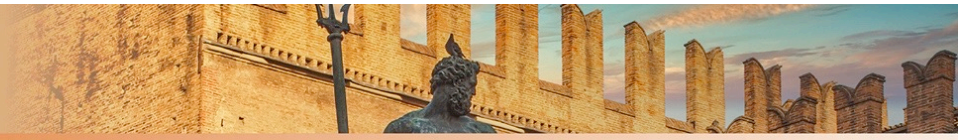
A recommended practical approach to the management of anthracycline-based chemotherapy cardiotoxicity: an opinion paper of the working group on drug cardiotoxicity and cardioprotection, Italian Society of Cardiology

Paolo Spallarossa[a], Nicola Maurea[b], Christian Cadeddu[c], Rosalinda Madonna[d], Donato Mele[e], Ines Monte[f], Giuseppina Novo[g], Pasquale Pagliaro[h], Alessia Pepe[i], Carlo G. Tocchetti[j], Concetta Zito[k] and Giuseppe Mercuro[c]

Le tre maggiori classi di farmaci che inducono cardiotossicità sono:

- Antracicline
- Farmaci anti-Her-2
- Gli inibitori della tirosin chinasi

Le Antracicline sono il perno del trattamento di numerose patologie oncologiche, sia tumori solidi (k mammella, gastrico, sarcoma) che ematologici (leucemia acuta e cronica, linfoma di Hodgkin e non Hodgkin, mieloma multiplo).
L'uso in terapia delle antracicline è limitato da una cardiotossicità dose-correlata che può alla lunga determinare una forma severa e irreversibile di cardiomiopatia.
E' questa la ragione per cui è necessaria la stretta collaborazione tra cardiologo ed oncoematologo.



Potenziale tossicità cardiaca indotta dagli agenti chemioterapici d'uso comune

Cardiotoxicity of Anticancer Treatments: Epidemiology, Detection, and Management

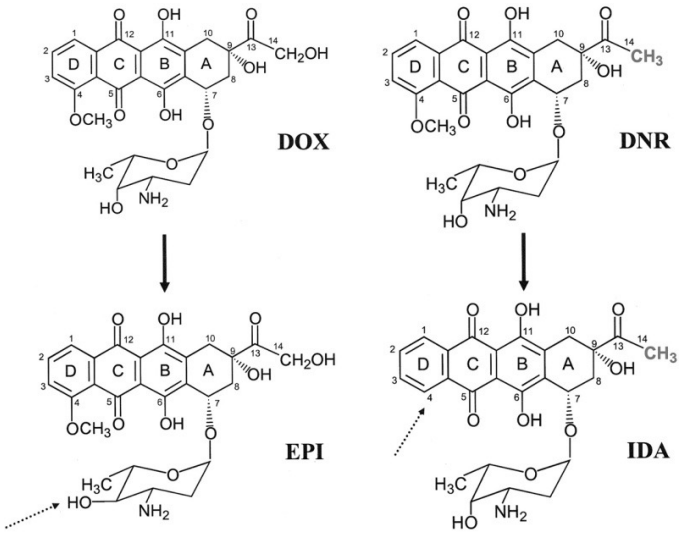
Giuseppe Curigliano, MD, PhD[1]; Daniela Cardinale, MD, PhD[2]; Susan Dent, MD[3]; Carmen Criscitiello, MD, PhD[1]; Olexiy Aseyev, MD, PhD[3]; Daniel Lenihan, MD[4]; Carlo Maria Cipolla, MD[2]

CA CANCER J CLIN 2016;66:309–325

Incidence

- Common= > 5%
- Intermediate= 1%-5%
- Uncommon=<1%

DRUG	STUDY	TOXIC DOSE RANGE	CARDIAC TOXICITY	FREQUENCY OF OCCURRENCE[a]
Doxorubicin	Chlebowski 1979[30]	> 450 mg/m^2	Left ventricular dysfunction	Common
Epirubicin	Tjuljandin 1990[31]	> 900 mg/m^2		Common
Idarubicin	Anderlini 1995[32]	150-290 mg/m^2		Intermediate
Paclitaxel	Perez 1998[33]	Conventional dose	Left ventricular dysfunction	Intermediate
Docetaxel	Kenmotsu & Tanigawara 2015[34]			Intermediate
Cyclophosphamide	Gottdiener 1981,[35] Goldberg 1986[36]	>100-120 mg/kg	Left ventricular dysfunction	Intermediate
Ifosfamide	Kandylis 1989,[37] Tascilar 2007,[38] Cancer Care Ontario[39]	>10 mg/m^2		Uncommon
Capecitabine	Sentürk 2009[40]	Conventional dose	Cardiac ischemia	Intermediate
Fluorouracil	Sentürk 2009,[40] Schimmel 2004,[41] Chanan-Khan 2004[42]			Intermediate
Paclitaxel	Perez 1998[33]	Conventional dose	Cardiac ischemia	Uncommon
Docetaxel	Kenmotsu & Tanigawara 2015[34]			Intermediate
Trabectedin	Lebedinsky 2011[43]	Conventional dose	Cardiac ischemia	Intermediate
Arsenic trioxide	Brana & Taberno 2010[44]	Conventional dose	QTc prolongation	Common
Paclitaxel	Perez 1998[33]	Conventional dose	QTc prolongation	Uncommon



0031-6997/04/5602-185–229$7.00
PHARMACOLOGICAL REVIEWS
Vol. 56, No. 2
40206/1155945
Printed in U.S.A
Pharmacol Rev 56:185–229, 2004

Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity

GIORGIO MINOTTI, PIERANTONIO MENNA, EMANUELA SALVATORELLI, GAETANO CAIRO, AND LUCA GIANNI

Department of Drug Sciences and Center of Excellence on Aging, G. d'Annunzio University School of Medicine, Chieti, Italy (G.M., P.M., E.S.); Institute of General Pathology, University of Milan School of Medicine, Milan, Italy (G.C.); and Unit of Medical Oncology, Istituto Nazionale Tumori, Milan, Italy (L.G.)

- Intercalazione nel DNA
- Inibizione topoisomerasi II
- Formazione ROS

Ca mammario
Sarcoma TM
Ca gastrico

USO CLINICO

Linfomi
Mieloma multiplo
Leucemie

Ipotesi di danno cardiaco da antracicline

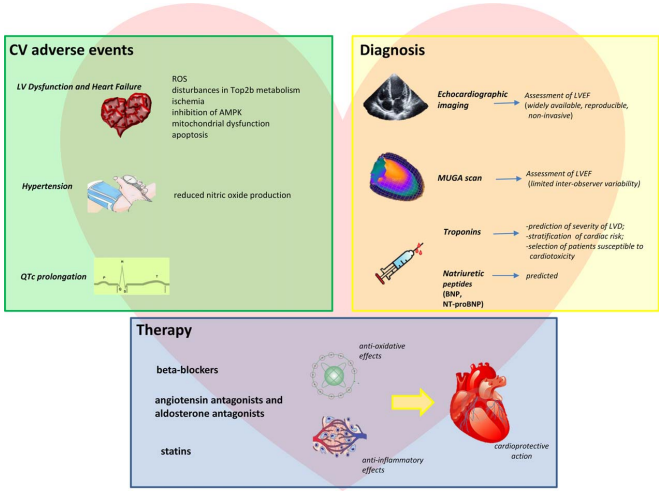
Disfunzione contrattile del ventricolo sx (left ventricular dysfunction)

Perdita della funzione contrattile dei cardiomiociti per meccanismi di apoptosi (forse l'inibizione della topoisomerasi 2b è causa di rotture nel doppio filamento di DNA il che determina difetti nella genesi mitocondriale e aumento dei ROS con morte dei cardiomiociti)

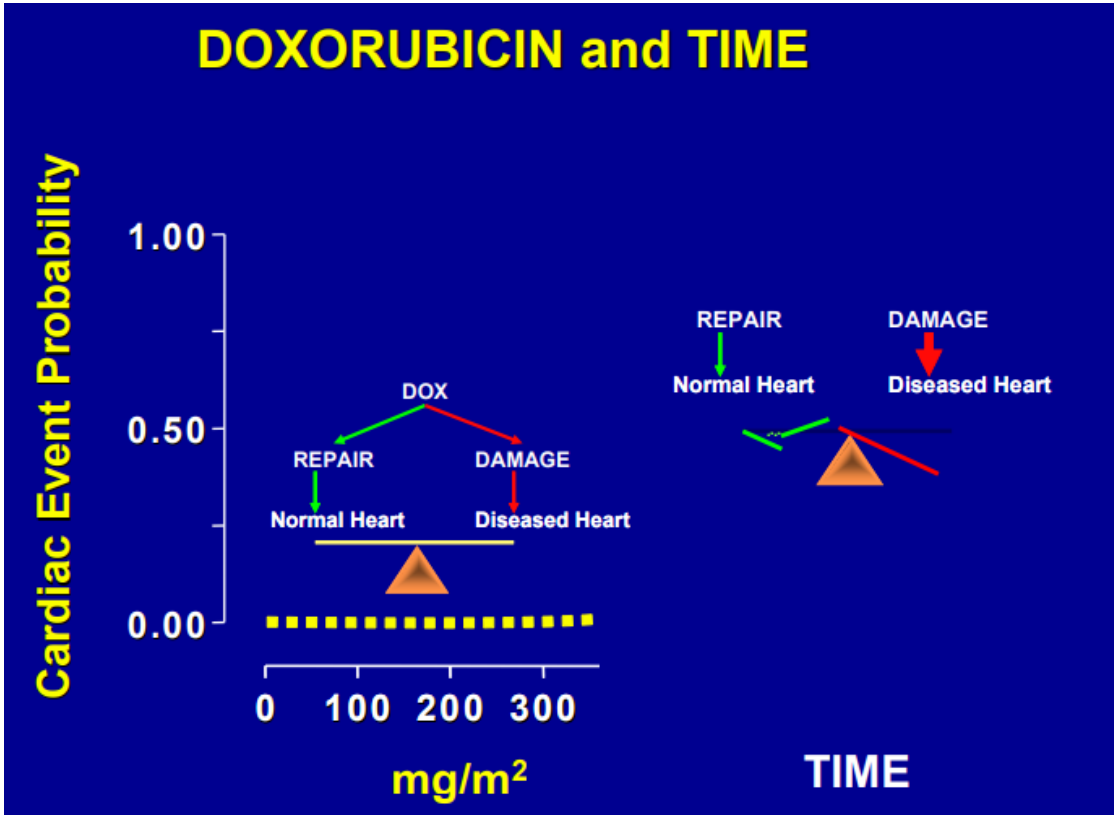
Formazione di complessi marziali e di ROS che risultano in disfunzione mitocondriale

Alterazioni dell'omeostasi calcica

Effetto sui progenitori cardiaci?



DANNO TARDIVO/CRONICO (anche ad 1 anno o molto tardiva)
Rilevante, correlato alla dose cumulativa e sommantesi all'aging, all'effetto della RT toracica, a preesistenti condizioni di rischio come l'ipertensione



Giorgio Minotti et al. Pharmacol Rev 2004;56:185-229

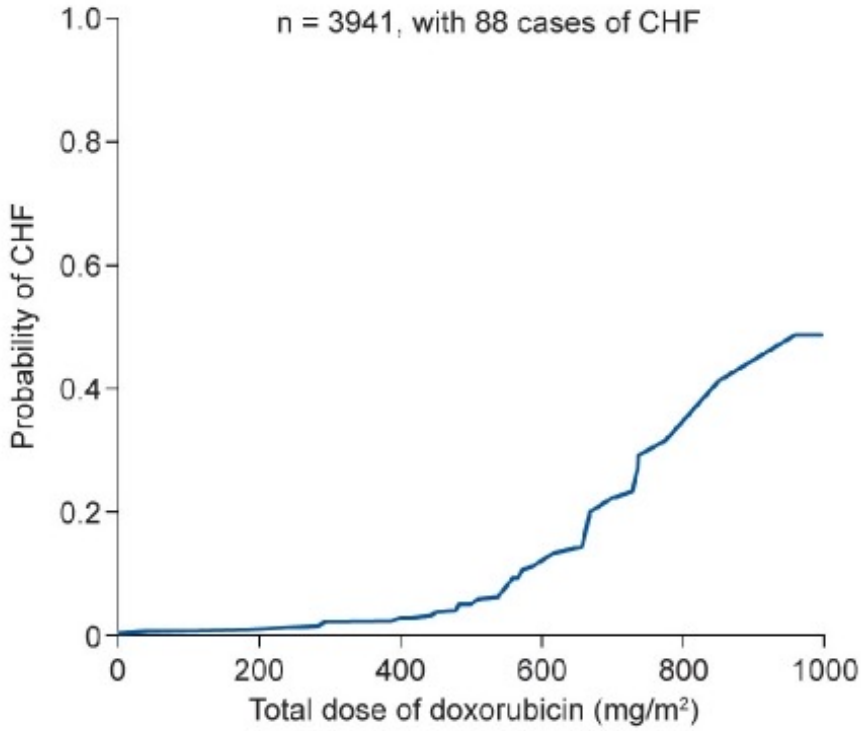
Evento più frequente
disfunzione ventricolare sinistra moderata ed asintomatica

- possibile evoluzione a forme severe
- richiede un monitoraggio clinico-strumentale e trattamenti farmacologici mirati
- costi psicologici e socio-sanitari

Doxorubicina (o Adriblastina – Adriamicina)

Il rischio di scompenso cardiaco indotto da doxorubicina aumenta con la dose cumulativa:

- dal 3% al 5% con 400 mg/m2,
- dal 7% al 26% con 550 mg/m2,
- dal 18% al 48% con 700 mg/m2



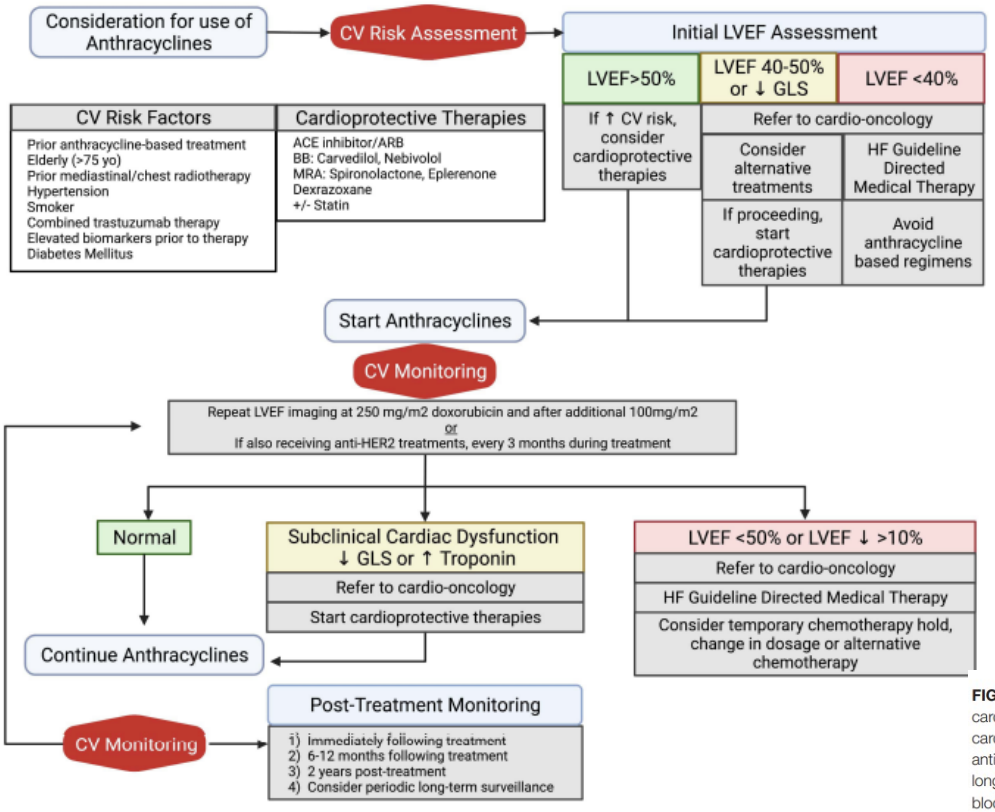
Von Hoff, Ann Intern Med 1979

Epirubicina

- Analogo di seconda generazione
- Migliora l'indice terapeutico
- Non riduce il rischio di sviluppare cardiomiopatia

	Dose soglia (mg/mq)
- Doxorubicina	450-550
- Epirubicina	850-1000

Algoritmo per la gestione del danno cardiaco da antracicline



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REVIEW
published: 22 April 2022
doi: 10.3389/fcvm.2022.863314

Novel Therapeutics for Anthracycline Induced Cardiotoxicity

*Jacqueline T. Vuong[1], Ashley F. Stein-Merlob[2], Richard K. Cheng[3] and Eric H. Yang[2,4]**

[1] Department of Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, CA, United States, [2] Division of Cardiology, Department of Medicine, Ronald Reagan UCLA Medical Center, Los Angeles, CA, United States, [3] Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA, United States, [4] UCLA Cardio-Oncology Program, Division of Cardiology, Department of Medicine, University of California, Los Angeles, Los Angeles, CA, United States

Adapted from ESMO 2020 guidelines

FIGURE 3 | Algorithm of clinical management for prevention and treatment of anthracycline induced cardiotoxicity. All patients should undergo baseline cardiovascular risk assessment, including an echocardiogram. Initiation of cardioprotective medications should be considered in patients with increased cardiovascular risk or abnormal baseline LVEF assessment. Patients with high-risk anthracycline therapy due to high dose (250 mg/m^2 doxorubicin) and concomitant anti-HER2 treatments should undergo serial cardiovascular monitoring during treatment. All patients should undergo post-treatment LVEF monitoring for detection of long-term cardiovascular sequelae. Adapted from ESMO 2020 guidelines (75). ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BB beta blocker; CV, cardiovascular; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist. Created with BioRender.com.

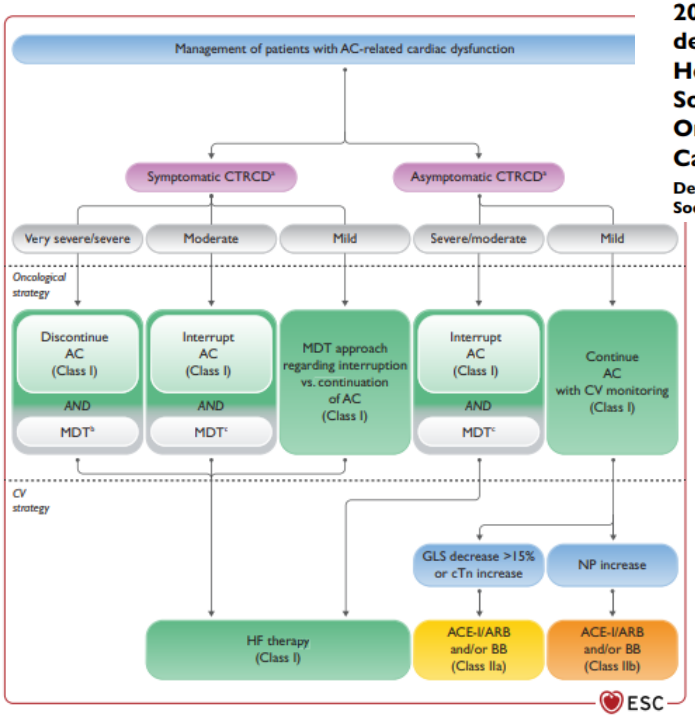

Figure 25 Management of anthracycline chemotherapy-related cardiac dysfunction. AC, anthracycline chemotherapy; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; cTn, cardiac troponin; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular; GLS, global longitudinal strain; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MDT, multidisciplinary team; NP, natriuretic peptides. [a]See *Table 3* (*Section 3*) for complete definition (symptomatic CTRCD: symptomatic confirmed HF syndrome; asymptomatic severe CTRCD: LVEF < 40%; asymptomatic moderate CTRCD: LVEF 40–49%; asymptomatic mild CTRCD: LVEF > 50%). [b]In rare exceptions, anthracycline chemotherapy may be restarted after recovery of LV function with optimal HF therapy. [c]A MDT discussion is recommended before restarting anthracycline chemotherapy after recovery of LV function.

ESC European Society of Cardiology
European Heart Journal (2022) **43**, 4229–4361
https://doi.org/10.1093/eurheartj/ehac244
ESC GUIDELINES

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)

Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC)

Supplement submission
OPEN

A recommended practical approach to the management of anthracycline-based chemotherapy cardiotoxicity: an opinion paper of the working group on drug cardiotoxicity and cardioprotection, Italian Society of Cardiology

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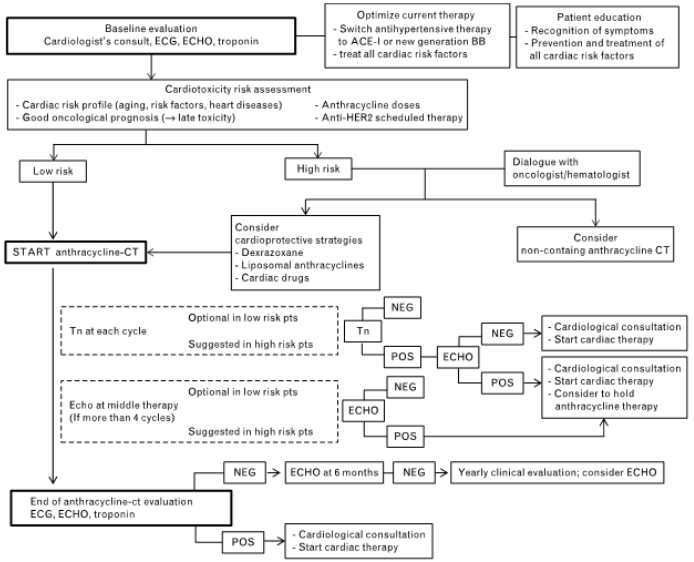
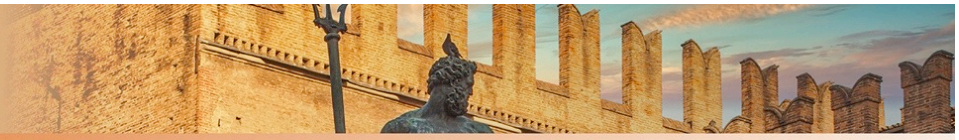
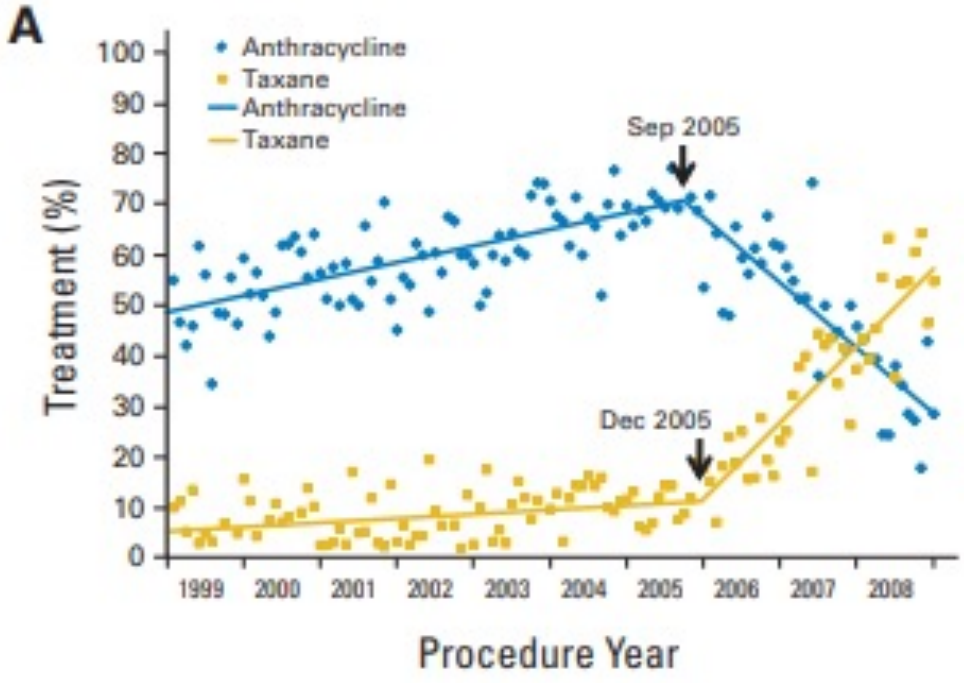


Prevenzione - Cardioprotezione

- Regimi terapeutici senza antracicline
- Antracicline meno cardiotossiche
- Farmaci cardioprotettivi
- Antracicline liposomiali



VOLUME 30 · NUMBER 18 · JUNE 20 2012
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT



Decline in the Use of Anthracyclines for Breast Cancer

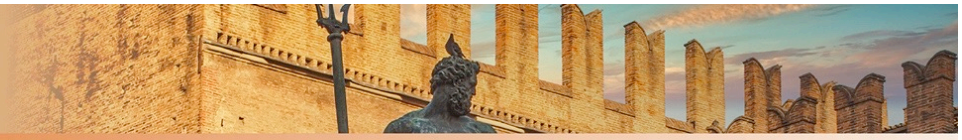
Sharon H. Giordano, Yu-Li Lin, Yong Fang Kuo, Gabriel N. Hortobagyi, and James S. Goodwin

Results

A total of 4,458 patients were included in the Medicare cohort and 30,422 in the private insurance cohort. After 2005, a sharp increase in the use of taxane-based chemotherapy and a decline in anthracycline-based chemotherapy was seen. By 2008 in the Medicare cohort, 51% of patients received taxane-based and 32% received anthracycline-based chemotherapy. By the end of 2008 the majority of patients younger than 65 years were also receiving taxane-based chemotherapy Patients younger than 35 years were less likely to be treated with a taxane-based regimen whereas patients who underwent 21-gene recurrence score testing and those treated with trastuzumab were more likely to receive taxane-based chemotherapy.

Conclusion

The use of anthracycline-based chemotherapy has declined, and the majority of patients with breast cancer are instead receiving taxane-based chemotherapy. The potential impact on patien outcomes is unknown.



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Treatment for Systolic Dysfunction

Prevention & Early Stage Therapies

Beta Blockers
ACE inhibitors/ Angiotensin Receptor Blockers
Angiotensin Receptor-Neprilysin Inhibitors
Mineralocorticoid Receptor Antagonists
Sodium-glucose Cotransport 2 Inhibitors

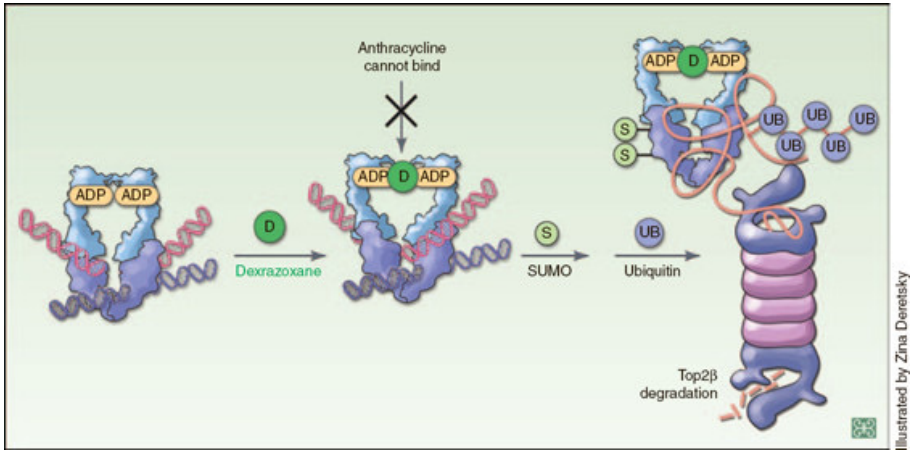
Dexrazoxane

Neurohormonal Therapies

Aerobic Exercise

Dexrazoxane

- Azione chelante sui complessi di Ferro ed effetto inibitorio sul legame Doxo-Topo IIB
- Dubbi sulla riduzione dell'efficacia delle antracicline
- Ipotizzato un effetto induttivo sullo sviluppo di seconde neoplasie
- Poco usato

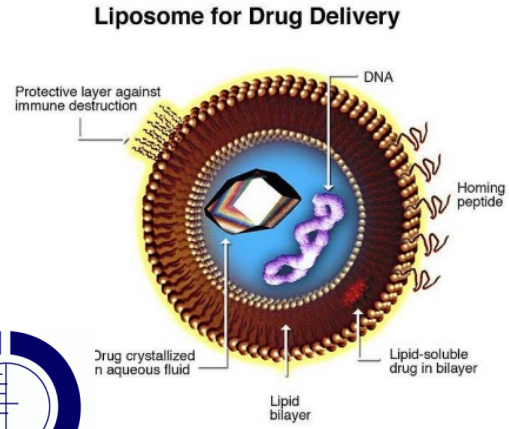


Antracicline liposomiali (peghilate e non-peghilate)

Different anthracycline derivates for reducing cardiotoxicity in cancer patients (Review)

van Dalen EC, Michiels EMC, Caron HN, Kremer LCM

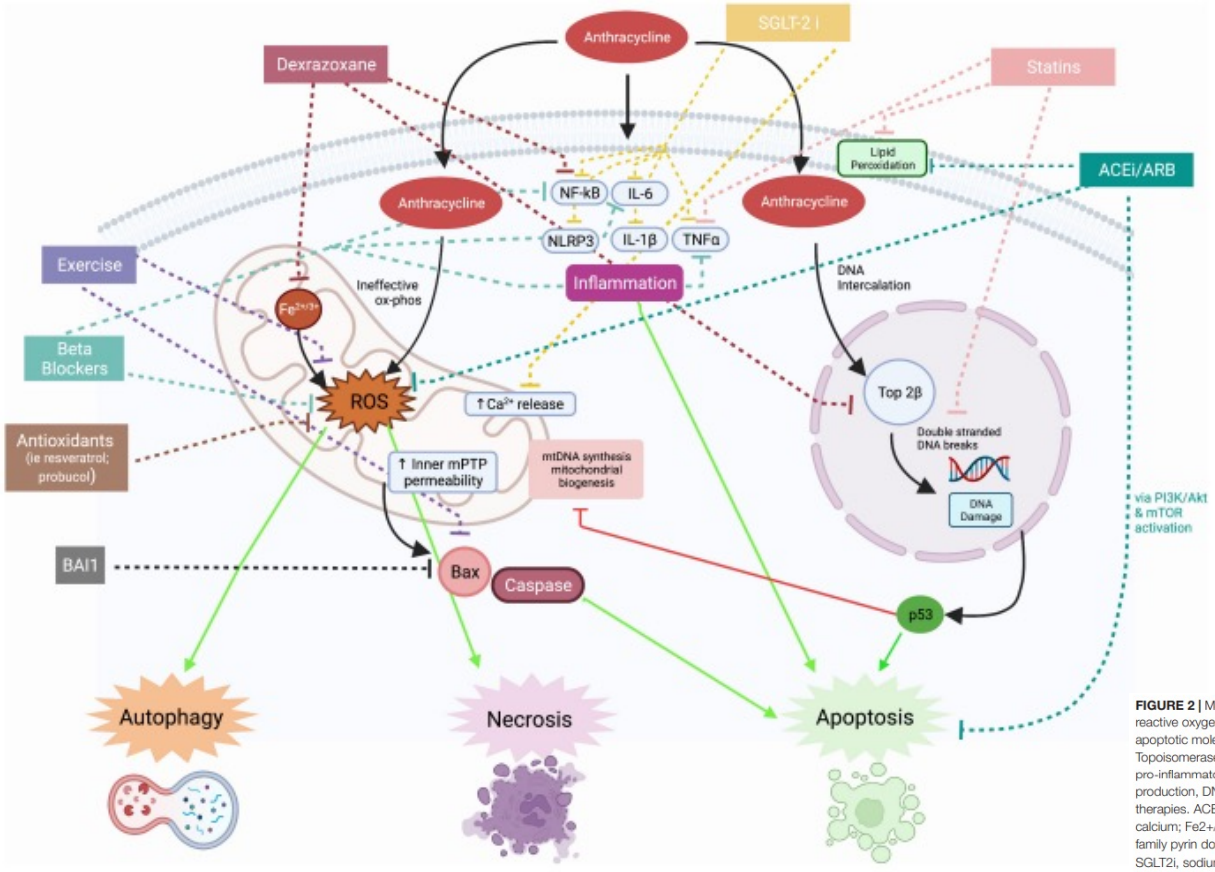
….. We conclude that in adults with a solid tumor liposomal-endocapsulated doxorubicin should be favoured over doxorubicin.



THE COCHRANE COLLABORATION®

2009

Preferite a quelle convenzionali nel ca mammario metastatico e rischio cardiaco



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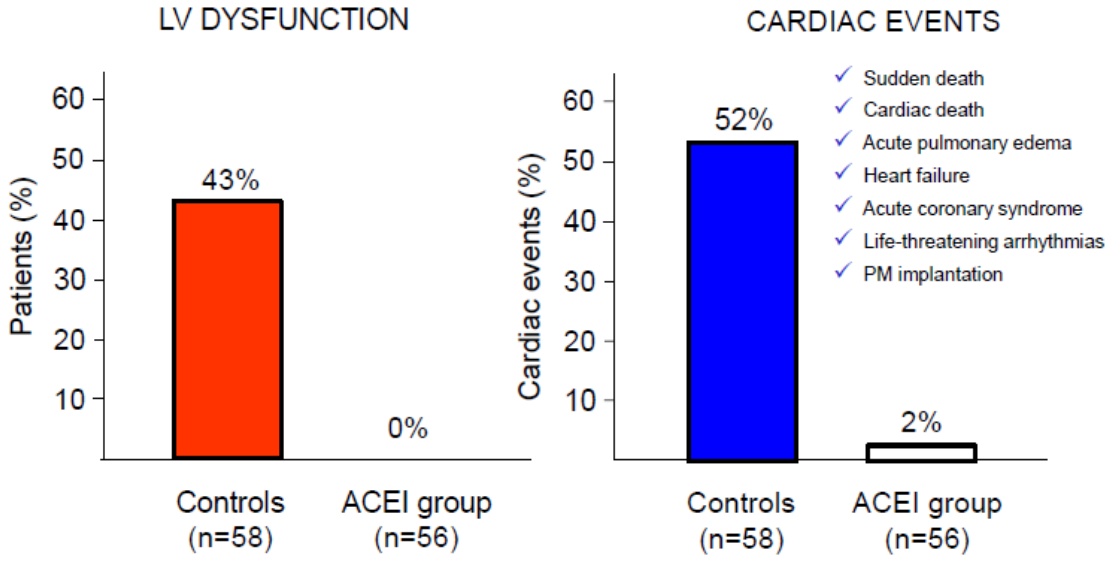
Beta Blockers	Mineralocorticoid Receptor Antagonists
ACE inhibitors/ Angiotensin Receptor Blockers	
Angiotensin Receptor-Neprilysin Inhibitors	Sodium-glucose Cotransport 2 Inhibitors

Neurohormonal Therapies

FIGURE 2 | Mechanisms of anthracycline cardiotoxicity and effects of therapies. Mitochondrial effects of anthracycline induced cardiotoxicity include production of reactive oxygen species, calcium dysregulation, impaired mitochondrial biogenesis, and disruption in mitochondrial membrane integrity, leading to release of apoptotic molecules such as bcl-2-associated X protein (Bax). The effects of anthracycline induced cardiotoxicity on nuclei include DNA intercalation and binding to Topoisomerase 2β to cause double stranded DNA breaks. DNA damage releases pro-apoptotic factors such as p53. Anthracyclines increase the expression of pro-inflammatory cytokines such as NF-kB, IL-6, NLRP3, IL-1β, and TNF-α. Proposed therapies have inhibitory effects on inflammation, reactive oxygen species production, DNA damage and apoptosis. Solid lines indicate mechanisms of anthracycline cardiotoxicity and dotted lines indicate mechanisms of proposed therapies. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BAI1, BAX activation inhibitor 1; Bax, bcl-2-associated X protein; Ca, calcium; Fe2+/3+, iron; IL, interleukin; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; NF-kB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; ox phos, oxidative phosphorylation; ROS, reactive oxygen species; TNFα, tumor necrosis factor alpha; Top2β, topoisomerase 2β; SGLT2i, sodium glucose cotransporter 2 inhibitor; PI3K, phosphinositide 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin. Created with BioRender.com.

ACE inibitori – Angiotensin receptor blockers

Enalapril riduce il rilascio di Troponina I con conseguente:



Cardinale, Circulation 2006

Cardio-prevenzione farmacologica

Brief Report

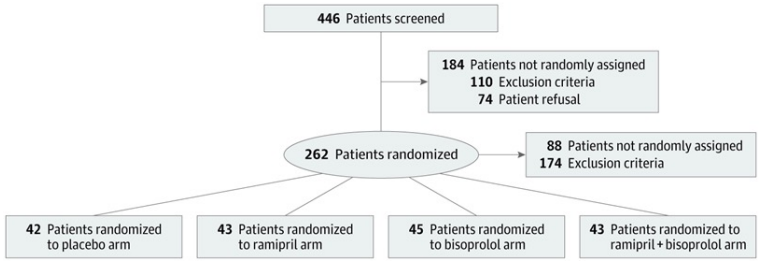
FREE

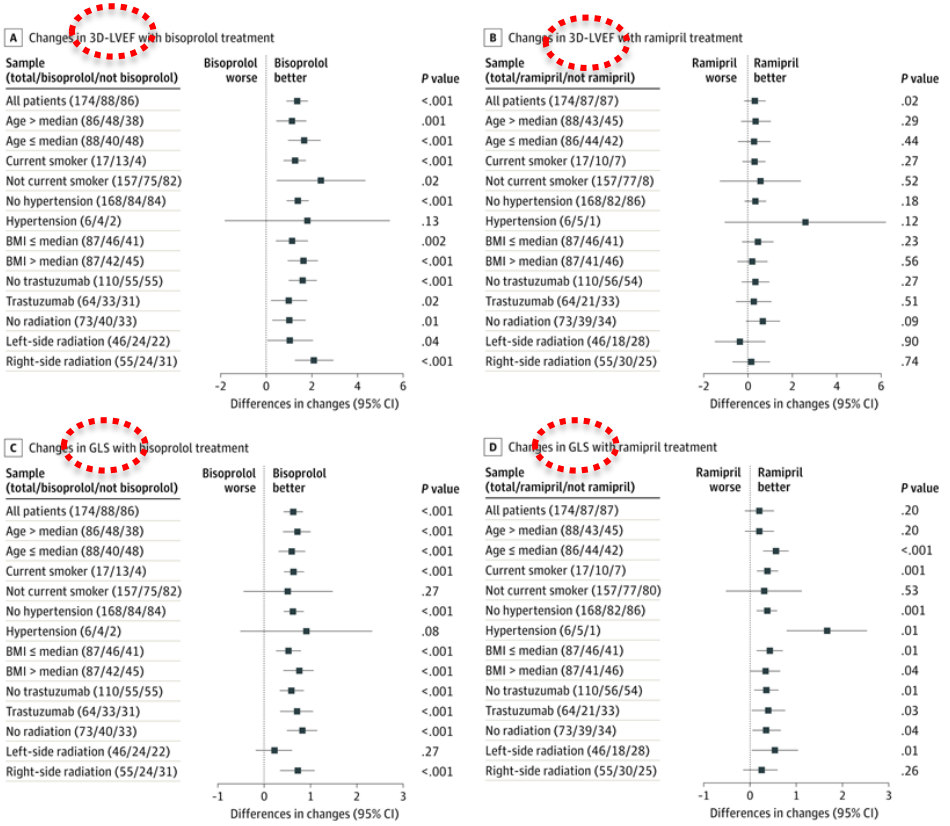
August 26, 2021

Cardioprotective Strategy for Patients With Nonmetastatic Breast Cancer Who Are Receiving an Anthracycline-Based Chemotherapy

A Randomized Clinical Trial

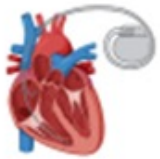
Lorenzo Livi, MD[1,2]; Giuseppe Barletta, MD[3]; Francesca Martella, MD[4]; et al





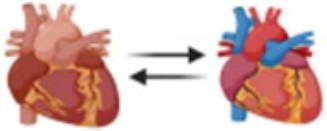
Treatment for Systolic Dysfunction

Moderate to End Stage Therapies



Cardiac Resynchronization Therapy

Mechanical Circulatory Support



Orthotopic Heart Transplantation

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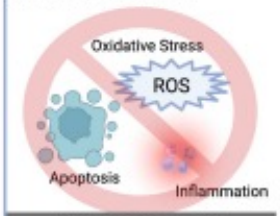
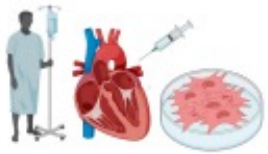
Future Directions



Mechanism-Specific Pharmacotherapies

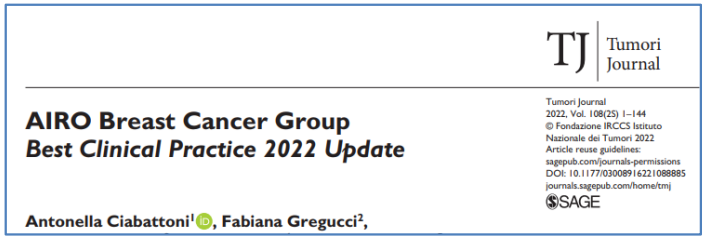


Stem Cell Therapy

Gene Therapy

Antracicline e Radioterapia

La RT non dovrebbe essere somministrata simultaneamente a trattamenti antiblastici che contengano derivati antraciclinici e/o taxani, in considerazione dell'aumentato rischio di effetti collaterali sui tessuti molli e cutanei, con possibile peggioramento del risultato estetico. Deve essere altresì essere considerato il potenziale aumento del rischio di tossicità polmonare e cardiaca, qualora sia irradiata la regione mammaria sinistra


TJ Tumori Journal

AIRO Breast Cancer Group
Best Clinical Practice 2022 Update

Tumori Journal
2022, Vol. 108(25) 1–144
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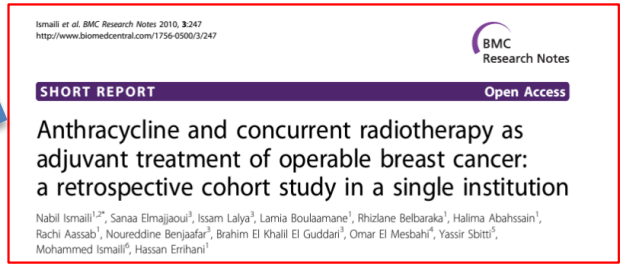
Antonella Ciabattoni[1], Fabiana Gregucci[2],

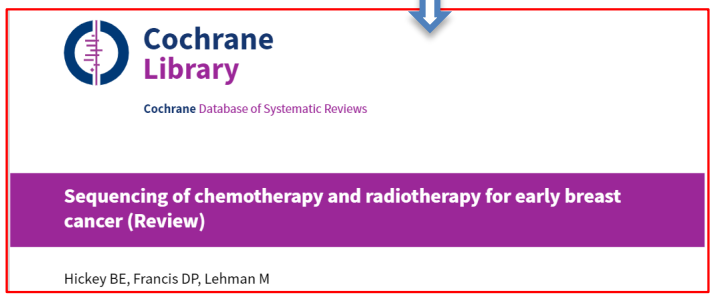

Ismaili et al. BMC Research Notes 2010, 3:247
http://www.biomedcentral.com/1756-0500/3/247

BMC Research Notes

SHORT REPORT Open Access

Anthracycline and concurrent radiotherapy as adjuvant treatment of operable breast cancer: a retrospective cohort study in a single institution

Nabil Ismaili[1,2*], Sanaa Elmajjaoui[3], Issam Lalya[3], Lamia Boulaamane[1], Rhizlane Belbaraka[1], Halima Abahssain[1], Rachi Aassab[1], Noureddine Benjaafar[3], Brahim El Khalil El Guddari[3], Omar El Mesbahi[4], Yassir Sbitti[5], Mohammed Ismaili[6], Hassan Errihani[1]


Cochrane Library

Cochrane Database of Systematic Reviews

Sequencing of chemotherapy and radiotherapy for early breast cancer (Review)

Hickey BE, Francis DP, Lehman M

Si ritiene indicato posticipare la RT al termine del trattamento sistemico

È consigliabile che il trattamento radiante venga avviato entro 4-6 settimane dal termine della chemioterapia, per non perdere l'efficacia dell'integrazione terapeutica

Antracicline e Radioterapia

Radiation-Related Heart Disease (RRHD)

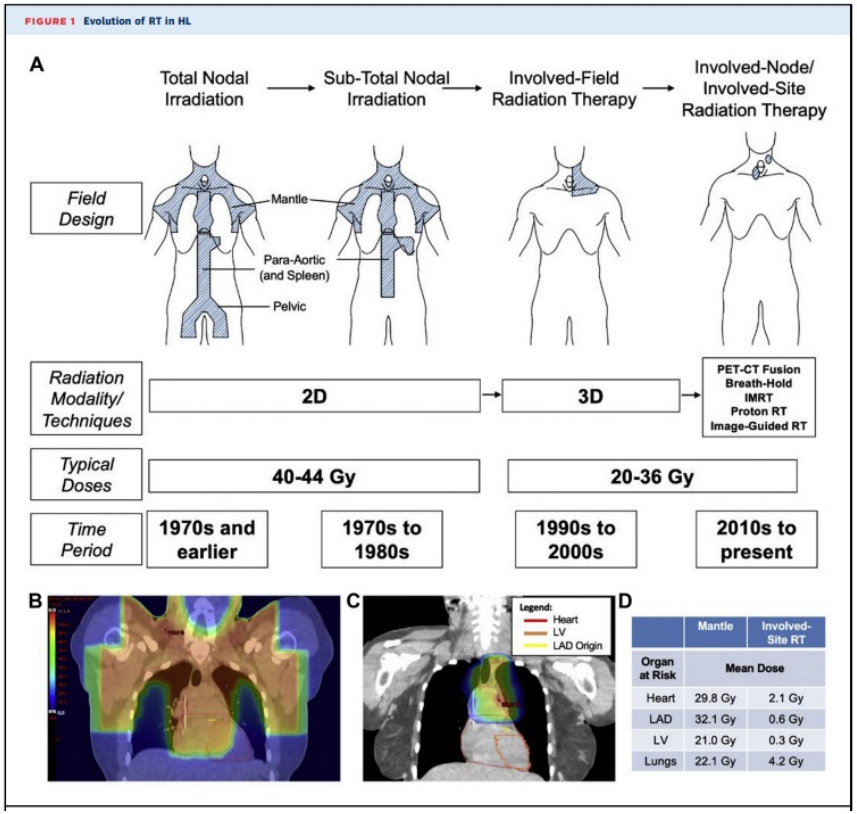
Radiation-Induced Heart Disease (RIHD)

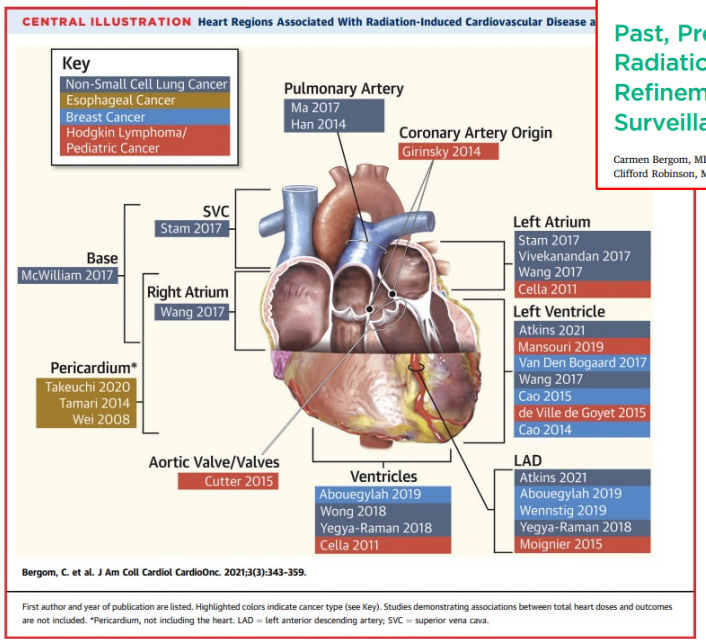
- Irradiazione torace anteriore o lato sinistro
- Alta dose cumulativa di radiazioni (> 30 Gy)
- Pazienti più giovani (<50 anni)
- Alta dose della frazione di radiazioni (> 2Gy/ day)
- Presenza ed estensione del tumore vicino al cuore
- Mancanza di schermatura
- Chemioterapia concomitante (le antracicline aumentano considerevolmente il rischio)
- Fattori di rischio cardiovascolari (diabete mellito, fumo, sovrappeso, ipertensione ≥ di moderata, ipercolesterolemia)
- Malattia cardiovascolare pre-esistente

Definizione di pazienti ad alto rischio: irradiazione del torace anteriore o del lato sinistro con ≥1 fattori di rischio per la RIHD

Lancellotti et al, European Heart Journal- Cardiovascular Imaging 2013

Radiation-Induced Heart Disease (RIHD)





JACC: CARDIOONCOLOGY VOL. 3, NO. 3, 2021

MINI-FOCUS ISSUE: RADIATION AND CARDIOVASCULAR DISEASE

STATE-OF-THE-ART REVIEW

Past, Present, and Future of Radiation-Induced Cardiotoxicity: Refinements in Targeting, Surveillance, and Risk Stratification

Carmen Bergom, MD, PhD,[a,b,c] Julie A. Bradley, MD,[d] Andrea K. Ng, MD, MPH,[e] Pamela Samson, MD, MPHS,[a,c] Clifford Robinson, MD,[a,c,f] Juan Lopez-Mattei, MD,[g] Joshua D. Mitchell, MD, MSCI[h,c,f]

Radiation-Induced Heart Disease (RIHD)
Coronary Artery Disease – CAD

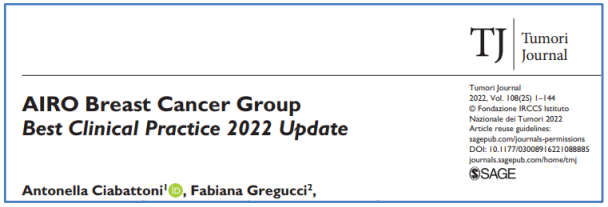
Raccomandazioni:

- la dose media cardiaca al di sotto dei 5 Gy
- la V25Gy del cuore inferiore al 5%
- la dose alla LAD al di sotto di 20 Gy

Frazionamento convenzionale

Ipofrazionamento moderato

- non vi sono dati dosimetrici definitivi che possano essere utilizzati come riferimenti certi
- dosi soglia biologicamente equivalenti


TJ Tumori Journal

AIRO Breast Cancer Group
Best Clinical Practice 2022 Update

Antonella Ciabattoni[1], Fabiana Gregucci[2],


The NEW ENGLAND JOURNAL of MEDICINE

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

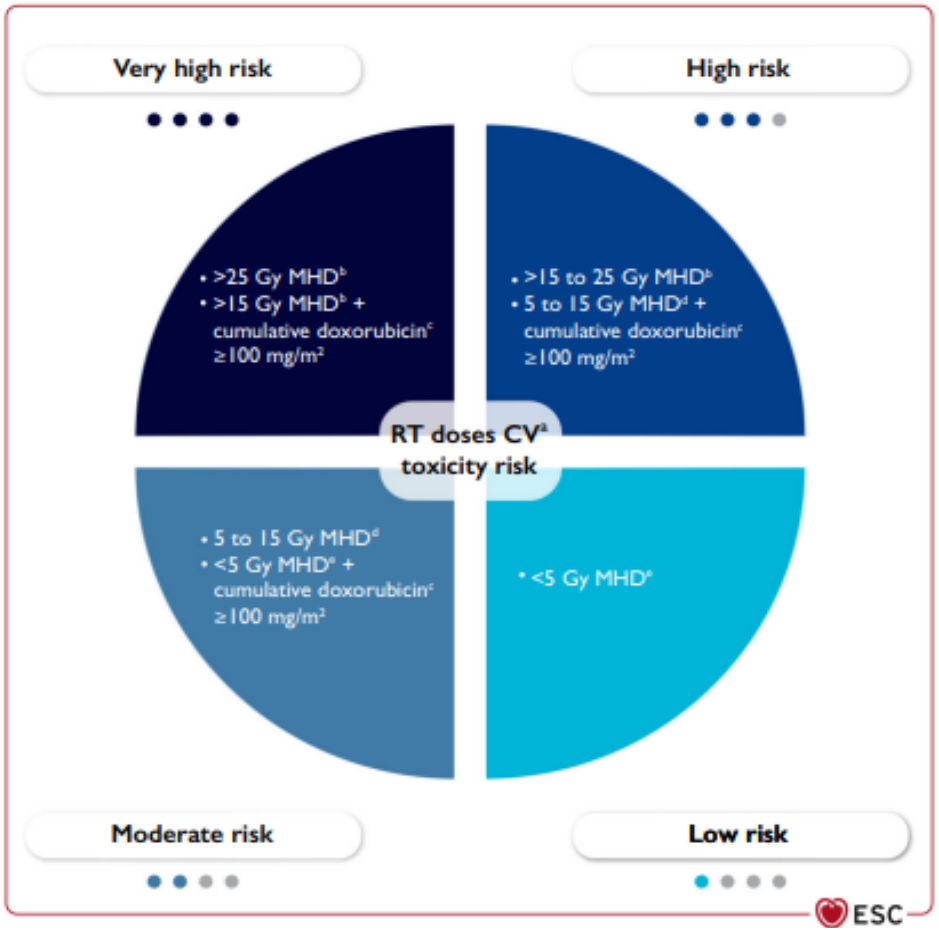
Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

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.

correlazione tra la dose media al cuore ed il rischio di eventi coronarici maggiori

⇩

+7.4% per ogni incremento di 1 Gy di MHD



Antracicline e Radioterapia

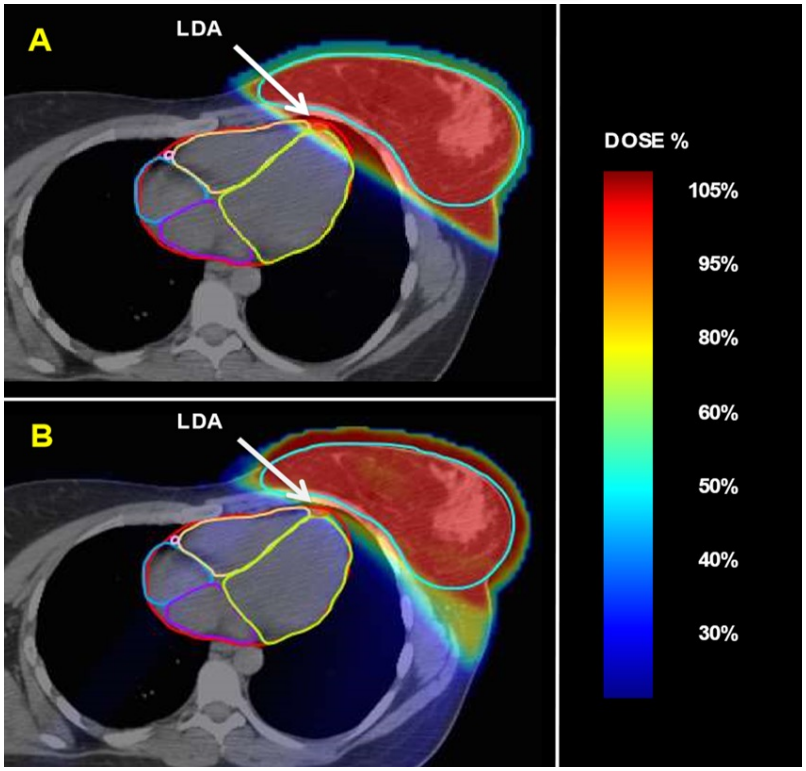
ESC European Society of Cardiology
European Heart Journal (2022) 43, 4229–4361
https://doi.org/10.1093/eurheartj/ehac244
ESC GUIDELINES

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)

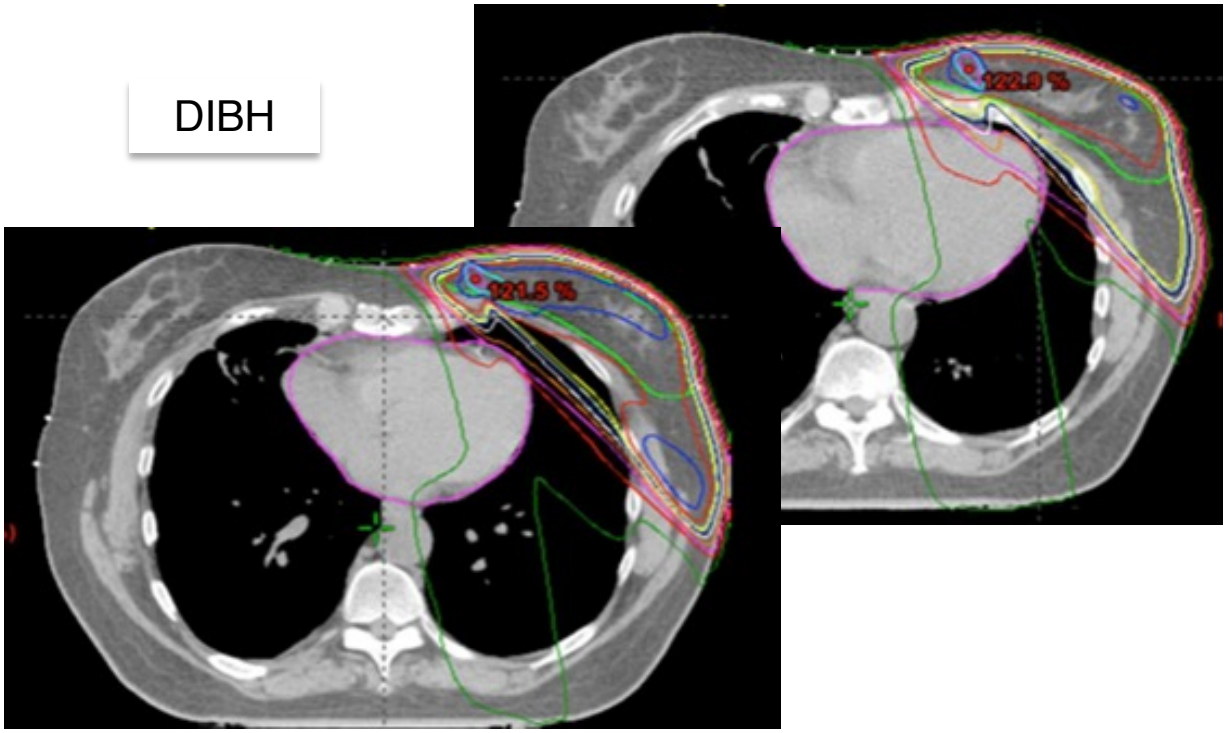
Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC)

Strategie di prevenzione

IMRT-VMAT



DIBH



Intensità modulata

Radiotherapy

Dosimetric Evaluation of Different Intensity-Modulated Radiotherapy Techniques for Breast Cancer After Conservative Surgery

Technology in Cancer Research & Treatment
2015, Vol. 14(5) 515–523

DOI: 10.1177/1533034614551873
tct.sagepub.com
SAGE

Fuli Zhang, PhD[1], Yadi Wang, MD, PhD[1], Weidong Xu, MM[1], Huayong Jiang, MM[1], Qingzhi Liu, MS[1], Junmao Gao, MM[1], Bo Yao, MM[1], Jun Hou, MM[1], and Heliang He, MM[1]

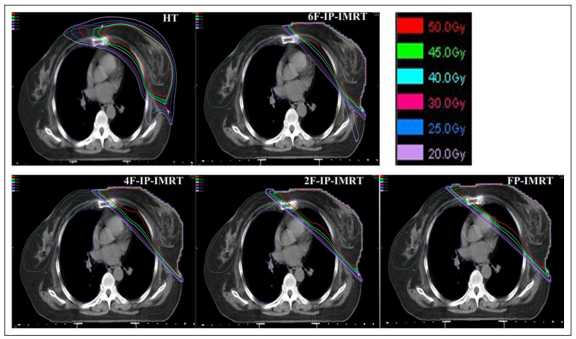
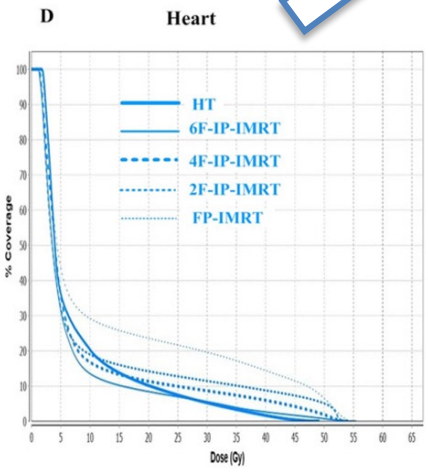


Figure 1. Isodose distributions of HT and 3 types of IP-IMRT and FP-FIF plans are shown for a typical patient. IP-IMRT indicates inverse-planned intensity-modulated radiotherapy; FP-FIF, forward-planned field in field; HT, helical tomotherapy.



I dati dosimetrici mostrano un **miglioramento significativo nella riduzione delle alte dosi al cuore, rispetto alla 3D-CRT**

Randomized Controlled Trial
Radiother Oncol. 2016 Dec;121(3):414-419.
doi: 10.1016/j.radonc.2016.08.021. Epub 2016 Sep 13.

Ten years results of the Canadian breast intensity modulated radiation therapy (IMRT) randomized controlled trial

Jean-Philippe Pignol [1], Pauline Truong [2], Eileen Rakovitch [3], Margriet G Sattler [4], Timothy J Whelan [5], Ivo A Olivotto [6]

La IMRT non può essere sempre raccomandata per ridurre gli effetti collaterali (**basse dosi** agli organi sani circostanti, possibile aumento delle sequele cardiopolmonari e di tumori secondari)

Deep Inspiration Breath-Hold (DIBH)

Review > Int J Radiat Oncol Biol Phys. 2016 Mar 1;94(3):478-92. doi: 10.1016/j.ijrobp.2015.11.049. Epub 2015 Dec 17.

Deep Inspiration Breath Hold-Based Radiation Therapy: A Clinical Review

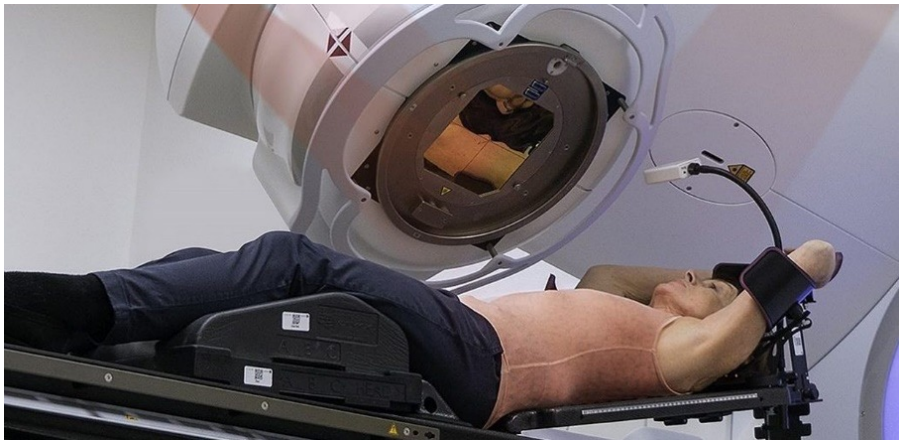
Judit Boda-Heggemann [1], Antje-Christin Knopf [2], Anna Simeonova-Chergou [3], Hansjörg Wertz [3], Florian Stieler [3], Anika Jahnke [3], Lennart Jahnke [3], Jens Fleckenstein [3], Lena Vogel [3], Anna Arns [3], Manuel Blessing [3], Frederik Wenz [3], Frank Lohr [3]

Journal of Medical Radiation Sciences
Open Access
REVIEW ARTICLE

The cardiac dose-sparing benefits of deep inspiration breath-hold in left breast irradiation: a systematic review

Lloyd M. Smyth, MMedRad (RT), BBiomed,[1,2] Kellie A. Knight, HScD, MHlthSc (RT), BAppSc (RT),[2] Yolanda K. Aarons, BAppSc (MedRad),[1] & Jason Wasiak, MPH[1]

[1]Epworth Radiation Oncology, Level 4, The Epworth Centre, Richmond, Victoria
[2]Department of Medical Imaging & Radiation Sciences, Faculty of Medicine, School of Biomedical Sciences, Nursing & Health Sciences, Monash University, Clayton, Victoria



Riduzione della MHD fino a 3,4 Gy

Riduzione del rischio di malattie cardiache del 13,6% e degli eventi coronarici maggiori del 25,2%

Protonterapia

Review > Cancer Treat Rev. 2018 Feb;63:19-27. doi: 10.1016/j.ctrv.2017.11.006.
Epub 2017 Nov 24.

Proton therapy for locally advanced breast cancer: A systematic review of the literature

Emmanuel Kammerer [1], Jennifer Le Guevelou [2], Abdulhamid Chaikh [3]
Julien Geffrelot [5], Christelle Levy [6], Eric Saloux [7], Jean-Louis Habrand

Abstract

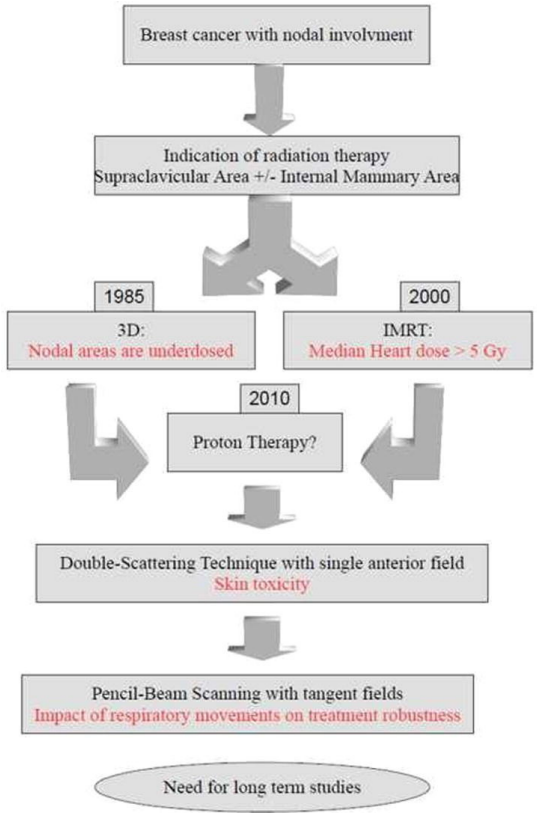
Background: Radiation therapy plays a major role in the management of adjuvant breast cancer with nodal involvement, with an iatrogenic increase of cardio-vascular risk. Photon therapy, even with intensity modulation, has the downsides of high mean heart dose and heterogeneous target coverage, particularly in the case of internal mammary irradiation. This systematic review of the literature aims to evaluate proton therapy in locally advanced breast cancer.

Material and methods: PubMed was searched for original full-text articles with the following search terms: «Proton Therapy» and «Breast Cancer». On-going trials were collected using the words "Breast Cancer" and "Protons".

Results: 13 articles met the criteria: 6 with passive proton therapy (Double Scattering), 5 with Pencil Beam Scanning (PBS) and 2 with a combination of both. Proton therapy offered a better target coverage than photons, even compared with intensity modulation radiation therapy (including static or rotational IMRT or tomotherapy). With proton therapy, volumes receiving 95% of the dose were around 98%, with low volumes receiving 105% of the dose. Proton therapy often decreased mean heart dose by a factor of 2 or 3, i.e. 1 Gy with proton therapy versus 3 Gy with conventional 3D, and 6 Gy for IMRT. Lungs were better spared with proton therapy than with photon therapy. Cutaneous toxicity observed with double scattering is improved with PBS.

Conclusion: Proton therapy reduces mean heart dose in breast cancer irradiation, probably reducing late cardio-vascular toxicity. Large clinical studies will likely confirm a clinical benefit of proton therapy.

Eccellente potenziale di minimizzare il rischio di eventi cardiaci, mantenendo la **MHD ⩽ 1 Gy**



Posizione Prona in Radioterapia mammaria

Research Letter

September 5, 2012

Prone vs Supine Positioning for Breast Cancer Radiotherapy

Silvia C. Formenti, MD; J. Keith DeWyngaert, PhD; Gabor Jozsef, Ph

» Author Affiliations | Article Information

JAMA. 2012;308(9):861-863. doi:10.1001/2012.jama.10759

Int. J

ELSEVIER

doi:10.1016/j.ijrobp.2008.10.045

› Int J Radiat Oncol Biol Phys. 2007 May 1;68(1):73-81. doi: 10.1016/j.ijrobp.2006.11.054. Epub 2007 Mar 6.

Long-term clinical outcomes of whole-breast irradiation delivered in the prone position

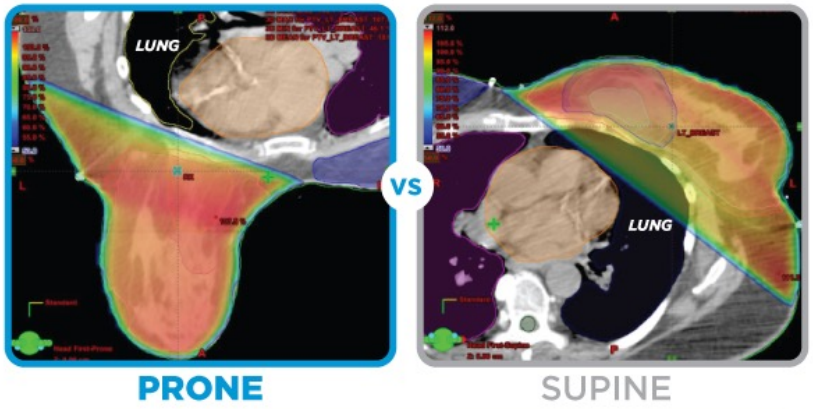
Lauren D Stegman [1], Katherine P Beal, Margie A Hunt, Monica N Fornier, Beryl McCormick

CLINICAL INVESTIGATION Breast

INDIVIDUAL POSITIONING: A COMPARATIVE STUDY OF ADJUVANT BREAST RADIOTHERAPY IN THE PRONE *VERSUS* SUPINE POSITION

ZOLTÁN VARGA, KATALIN HIDEGHÉTY, M.D.
LÁSZLÓ THURZÓ, M.D., PH.D., A

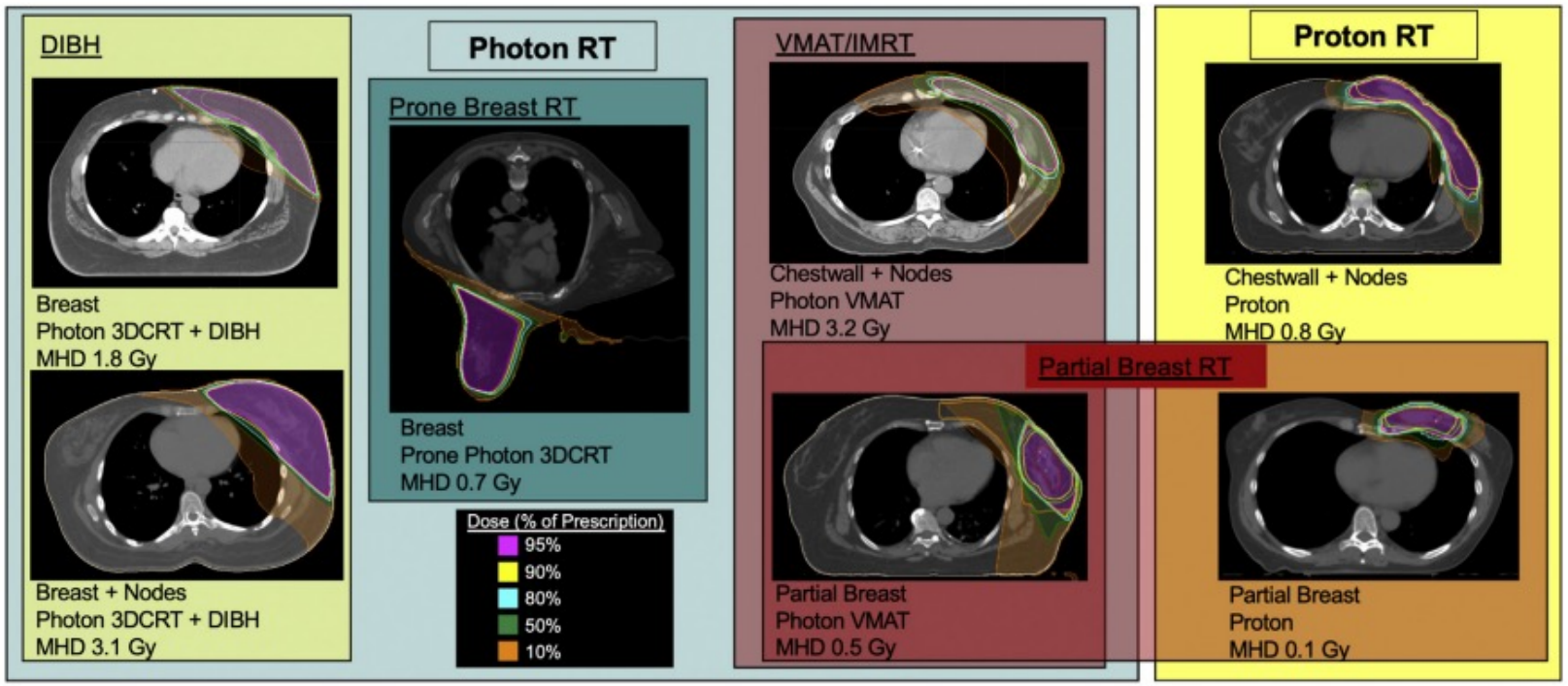
Department of Oncotherapy, Un

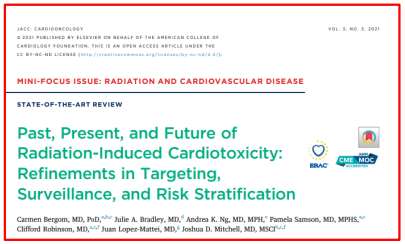


- copertura dosimetrica del volume target (PTV) significativamente migliore con il posizionamento supino rispetto a quello prono
- netta riduzione della dose al polmone in posizione prona
- dati non conclusivi relativamente alla dose alle cavità cardiache e alla LAD (**dislocazione anteriore**)
- riproducibilità inferiore rispetto a quelle in posizione supina, ad oggi maggiormente consolidate

Strategie di prevenzione

FIGURE 2 Example Breast Plans Using Different RT Techniques and Modalities




JACC: CARDIOONCOLOGY VOL. 3, NO. 3, 2021

MINI-FOCUS ISSUE: RADIATION AND CARDIOVASCULAR DISEASE

STATE-OF-THE-ART REVIEW

Past, Present, and Future of Radiation-Induced Cardiotoxicity: Refinements in Targeting, Surveillance, and Risk Stratification

Antracicline e Radioterapia: tossicità cutanea

TJ Tumori Journal

AIRO Breast Cancer Group
Best Clinical Practice 2022 Update

Tumori Journal
2022, Vol. 108(2S) 1–144
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DOI: 10.1177/03008916221088885
journals.sagepub.com/home/tmj
SAGE

Antonella Ciabattoni[1], Fabiana Gregucci[2],

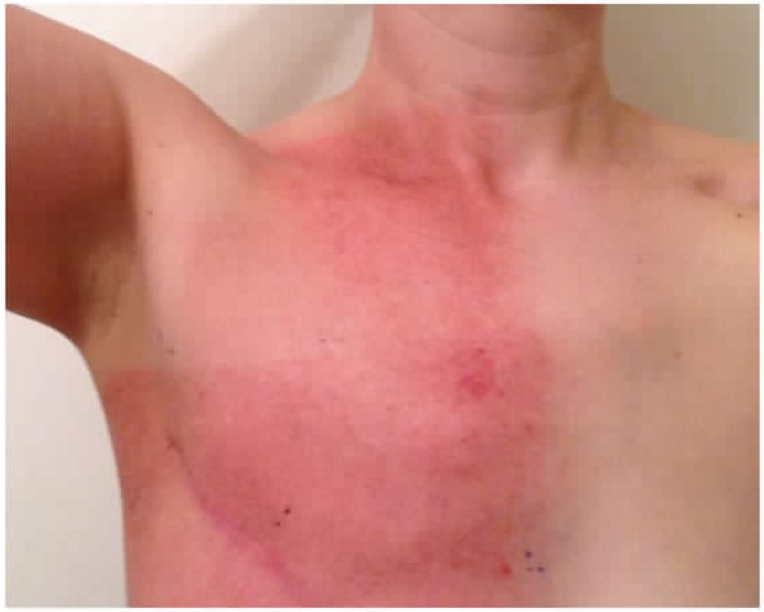
Dermatite da radiazioni

- determinata dal danno radioindotto a livello del tessuto dermo-epidermico
- può comparire entro 1-4 settimane dall'inizio del trattamento o manifestarsi più tardivamente generalmente entro 90 giorni dopo la fine dello stesso
- Il quadro si risolve generalmente entro 1 mese dal termine della radioterapia
- Gli effetti tardivi possono comparire ad almeno 3 mesi dal termine del trattamento e sono generalmente caratterizzati da fibrosi cutanea ed eventuale comparsa di teleangectasie
- Riduzione del risultato cosmetico e detrimento della qualità di vita dei pazienti

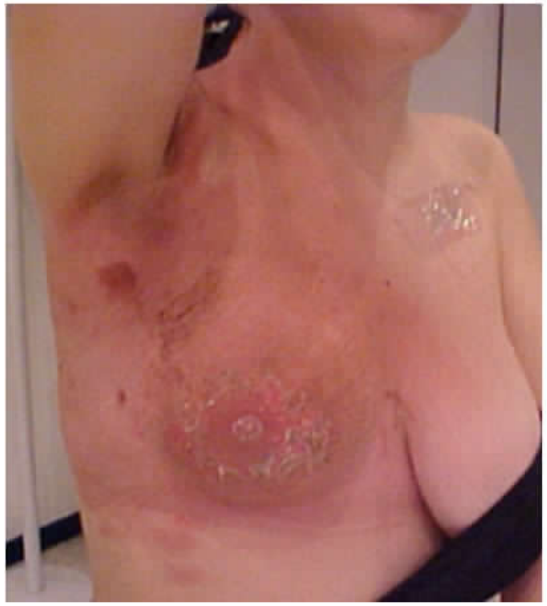
Fattori di rischi di tossicità cutanea

- la precedente terapia con antracicline e taxani risulta associata con lo sviluppo di tossicità acuta e tardiva e pertanto ne è sconsigliata la somministrazione concomitante con il trattamento radiante
- indicato intervallo di 4-6 settimane fra uso di antracicline e Radioterapia

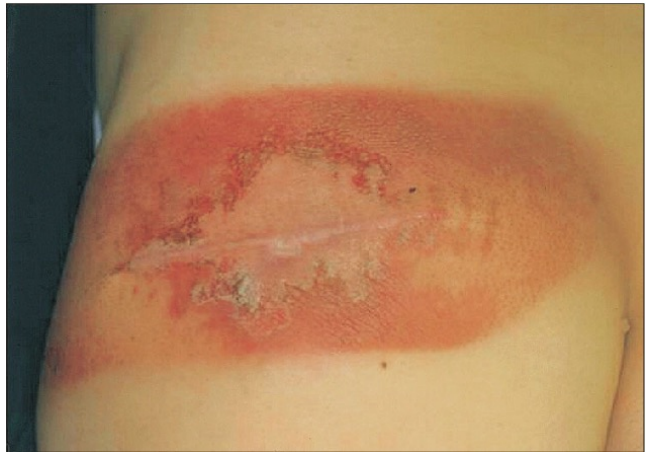
Tossicità cutanea

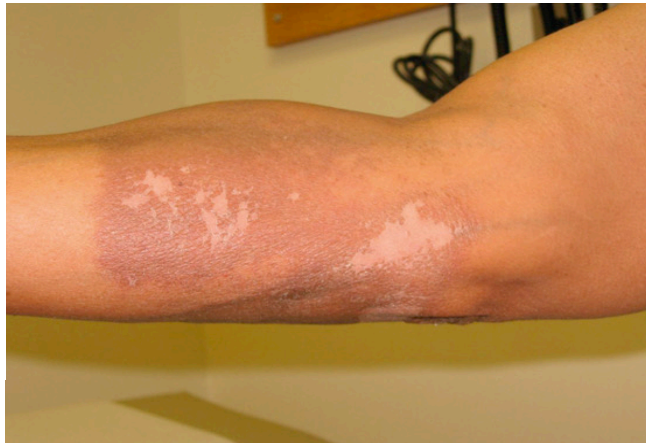


Grade 2 radiation dermatitis following external radiotherapy for breast cancer



Grade 3 radiation dermatitis following external radiotherapy for breast cancer





Tossicità cutanea - Sarcomi dei tessuti molli

- La **radioterapia preoperatoria che postoperatoria possono essere eseguite in modo concomitante o embricato con la chemioterapia**.
- Non esiste uno standard di cura
- La scelta dei farmaci chemioterapici e la concomitanza con la radioterapia deve essere oggetto delle **scelte multidisciplinari** del centro di riferimento.
- Qualora venga adottato il **trattamento sequenziale**, lo schema più comunemente utilizzato prevede: tre cicli di chemioterapia di induzione (rappresentata da una combinazione di *un'Antraciclina ed Ifosfamide*) seguita da trattamento radiante con dose convenzionale di *50 Gy* in frazioni giornaliere da 2 Gy, seguita eventualmente dalla chirurgia. Qualora si opti per il **trattamento concomitante** il regime più comunemente utilizzato nel periodo preoperatorio prevede l'uso della la radioterapia a partire dal primo o secondo ciclo chemioterapico, a dosi comprese tra 44 e 50 Gy in 25 frazioni giornaliere di 2 Gy.

Tossicità cutanea - Sarcomi dei tessuti molli

Table 2. Demographic and Clinical Characteristics and Toxicity Outcomes for the Patients Evaluated

Characteristic	Data (n = 303) No.	%
Local complications		
Yes	41	13.53
No	198	65.35
Missing	64	21.12
Local complications*		
Secondary operation	13	31.71
Readmission for wound care	5	12.20
Invasive procedure for wound management	3	7.32
Wound packing deep to dermis	6	14.63
> 6 weeks from wound breakdown	3	7.32
Missing	11	26.83

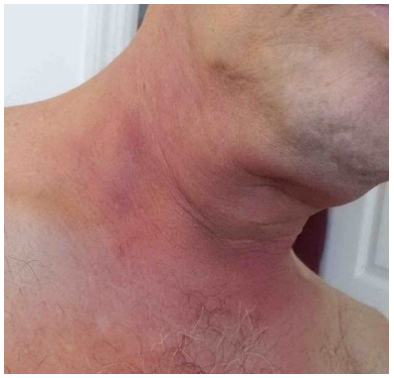
VOLUME 33 · NUMBER 31 · NOVEMBER 1 2015
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Feasibility of Preoperative Chemotherapy With or Without Radiation Therapy in Localized Soft Tissue Sarcomas of Limbs and Superficial Trunk in the Italian Sarcoma Group/ Grupo Español de Investigación en Sarcomas Randomized Clinical Trial: Three Versus Five Cycles of Full-Dose Epirubicin Plus Ifosfamide

Elena Palassini, Stefano Ferrari, Paolo Verderio, Antonino De Paoli, Javier Martin Broto, Vittorio Quagliuolo, Alessandro Comandone, Claudia Sangalli, Emanuela Palmerini, Antonio Lopez-Pousa, Rita De Sanctis, Stefano Bottelli, Michela Libertini, Piero Picci, Paolo G. Casali, and Alessandro Gronchi

These complications occurred in 26 patients (17.1%) when preoperative RT was added to chemotherapy. We observed that **patients treated with preoperative concurrent chemotherapy-RT had only limited worsening of toxicities** compared with patients receiving preoperative chemotherapy alone

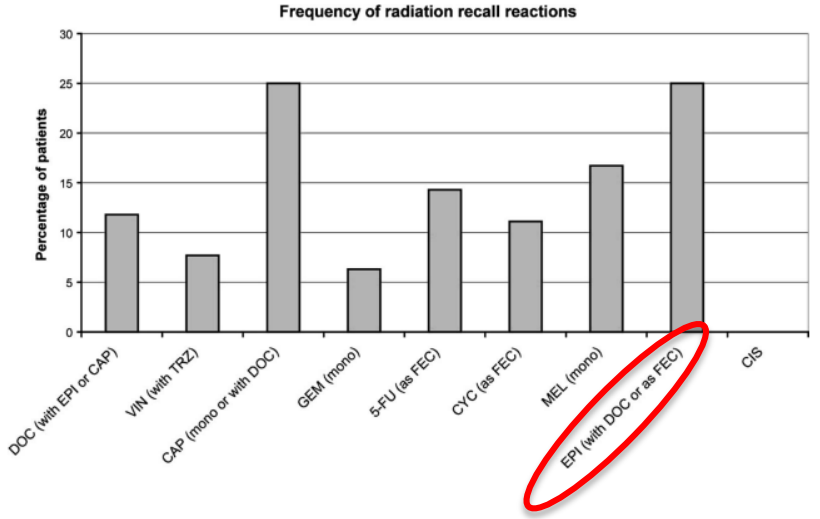
Radiation recall dermatitis



- Uncommon and **unpredictable phenomenon**
- **Acute inflammatory reaction** confined to previously irradiated areas that is triggered by the administration of precipitating systemic agents after radiation treatment
- It can occur **months or even many years** after irradiation
- The development of radiation recall is **drug-specific for any individual patient**, and it is not possible to predict which patients will react to which drugs
- The drugs for which radiation recall reactions have been most commonly reported include the **anthracycline** doxorubicin, the taxanes and the antimetabolites

Radiation Recall with Anticancer Agents

HOWARD A. BURRIS III, JANE HURTIG
Sarah Cannon Research Institute, Nashville, Tennessee, USA



GRAZIE PER L'ATTENZIONE