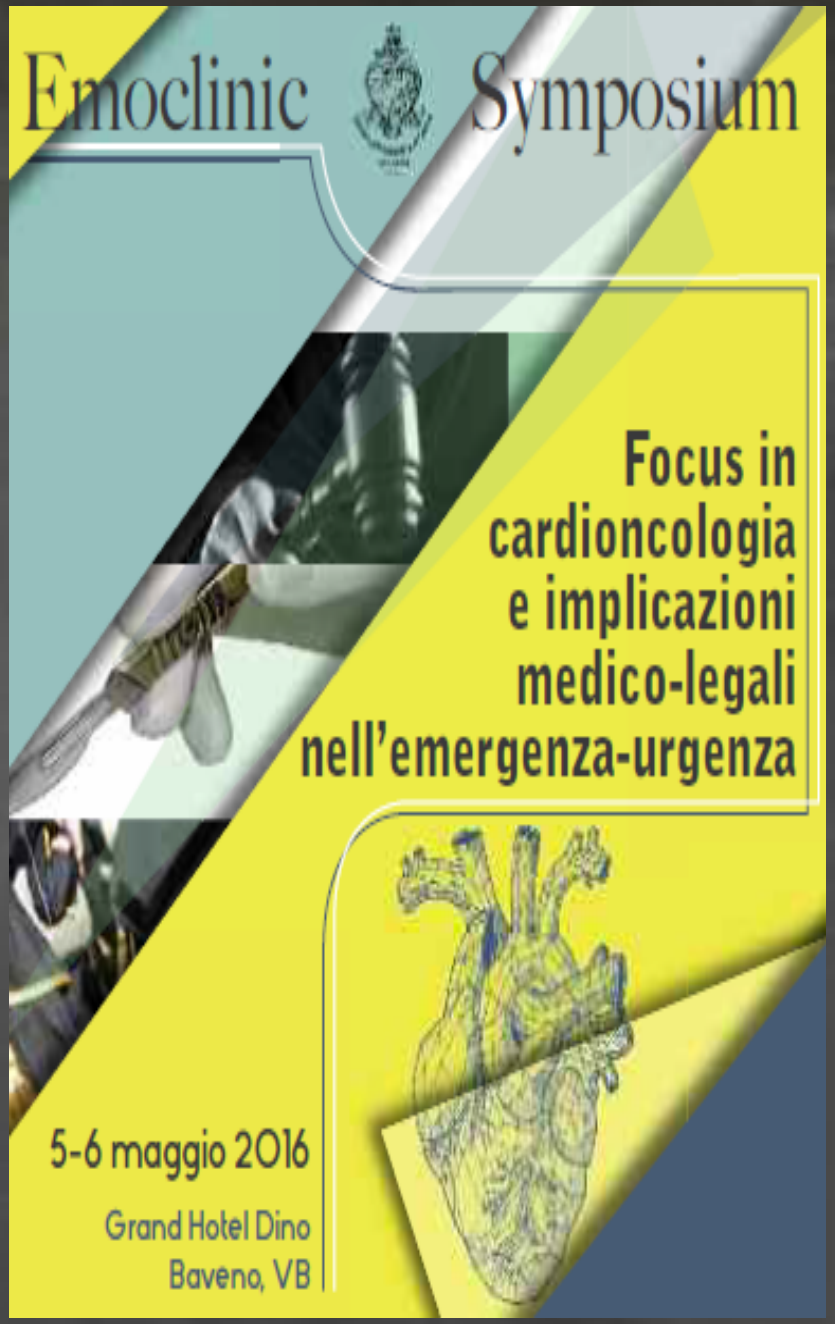


SEQUELE TARDIVE DI TRATTAMENTO RADIOTERAPICO

Dott.ssa Lidia Rossi

UTIC – AOU Novara

nato 1951

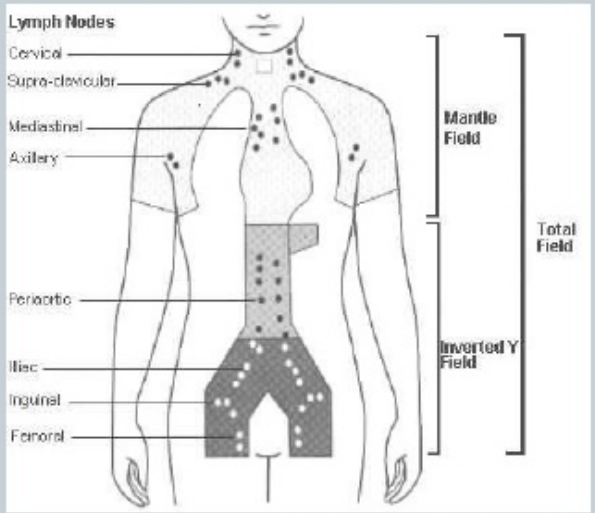
Familiarità per C.I.
Pregresso tabagismo

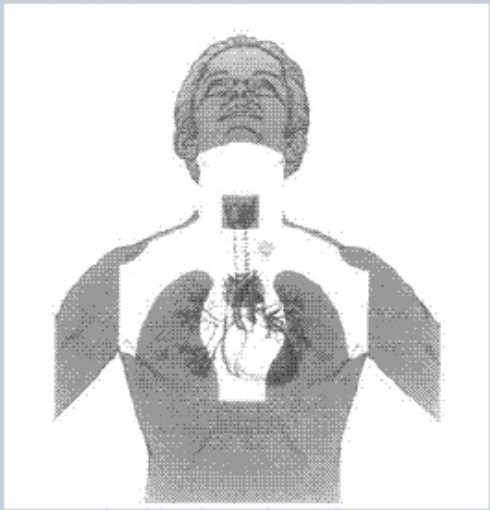
All' età di 5 aa fratt
Pregressa appendice

All' età di 22 an

MOPP	mecloretamina (giorno 0 e 7), vincristina (giorno 0 e 7), procarbazina (giorni 0-13), prednisone (giorni 0-13)

- Historical mantle field and total nodal irradiation





All' età di 31 anni (1982) recidiva di malattia di Hodgkin a localizzazione retroauricolare:

radioterapia

nato 1951

. . .

. 1974 Intervento di viscerolisi per occlusione intestinale acuta da briglie aderenziali

• 1989 colecistectomia per litiasi biliare

• 1981 pielolitotomia renale destra

• 1991- 1999 - 2008 litotrissia extraxorporea per calcolosi renale bilaterale con recidive a destra

. . .

nato 1951

- **Epatite cronica HCV correlata > interferone e ribavirina**
- **Ipotiroidismo iatrogeno in tp sostitutiva**

Int J Radiat Oncol Biol Phys 1995 Mar 30;31(5):1165-70.
Thyroid abnormalities after therapeutic external radiation.

Cancer radiother 2010 Jul;14(4-5):307-11.
Normal tissue tolerance to external beam radiation therapy: thyroid

The **thyroid gland** is **one of the organs most likely to produce clinically significant abnormalities after therapeutic external radiation.**

Radiation doses to the thyroid that **exceed approximately 26 Gy** frequently **produce hypothyroidism**, which may be clinically overt or subclinical
mainly a late effects occurring **beyond 6 months**,
its **incidence** is approximately **20 to 30%**
it can occur after **more than 25 years after radiation exposure**.

Silent thyroiditis, cystic degeneration, benign adenoma, and thyroid cancer
(risk for well-differentiated, papillary, and follicular thyroid cancer from **15- to 53-fold**)
have been observed **after therapeutically relevant doses of external radiation** .

Thyroid cancer increases with follow-up duration.

nato 1951

.....

- 2004 stenosi carotidea attinica trattata con bypass carotido-carotideo bilaterale

  stenosi arteria renale destra trattata con PTA + STENT

  stenosi succlavia sinistra trattata con PTA

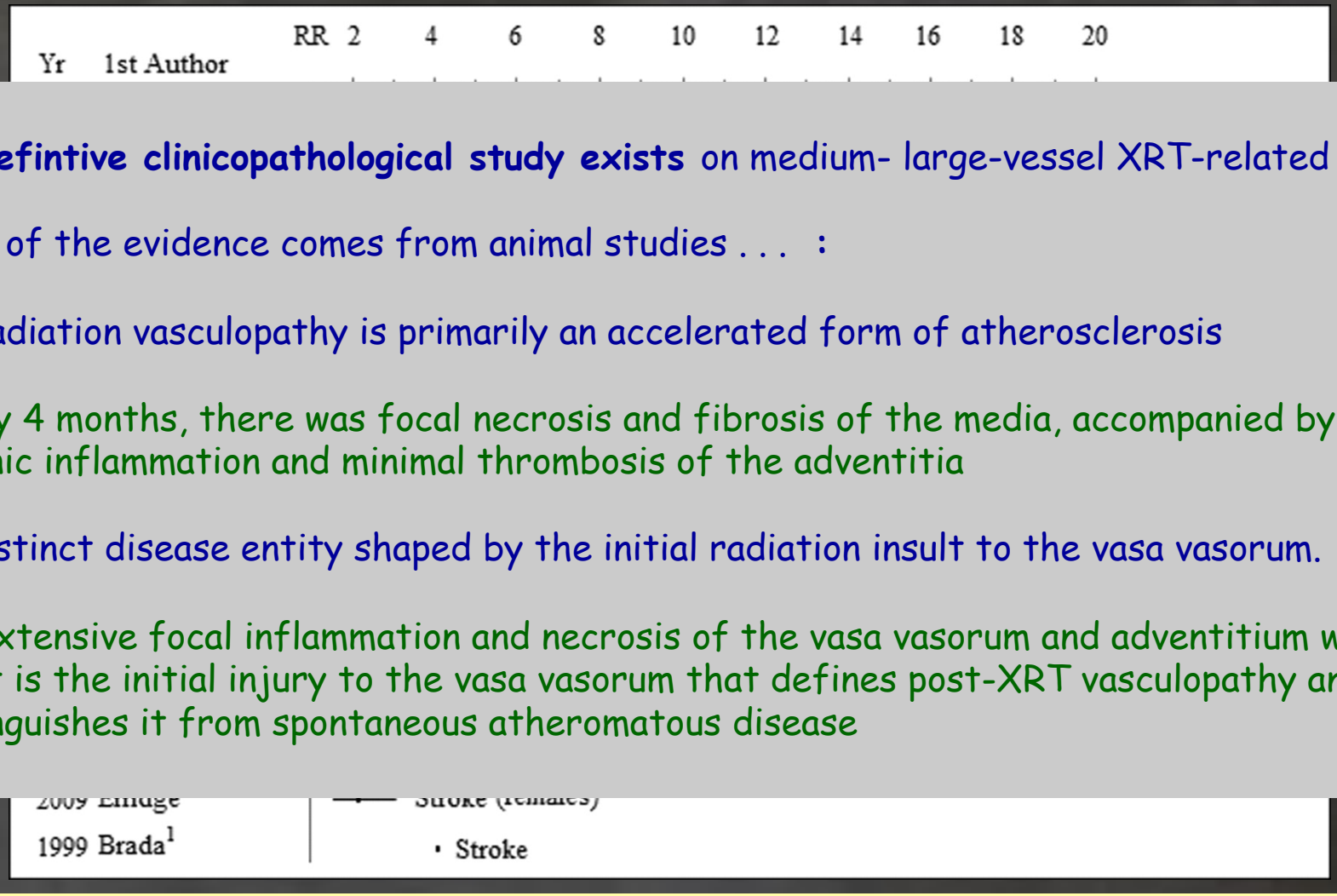
- 2014 restenosi intrastent su arteria renale destra sottoposta a re PTA

  stenosi arteria iliaca sinistra trattata con PTA e stent

- RESIDUANO STENOSI DI ARTERIA MESENTERICA SUPERIORE, IPOGASTRICA, SUCCLAVIA DESTRA

Relative risk (RR) of stroke and transient ischemic attack (TIA) after head and/or neck radiotherapy.

Chris Plummer et al. Stroke. 2011;42:2410-2418



No defintive clinicopathological study exists on medium- large-vessel XRT-related disease.

Most of the evidence comes from animal studies . . . :

1. radiation vasculopathy is primarily an accelerated form of atherosclerosis

By 4 months, there was focal necrosis and fibrosis of the media, accompanied by chronic inflammation and minimal thrombosis of the adventitia

2. distinct disease entity shaped by the initial radiation insult to the vasa vasorum.

Extensive focal inflammation and necrosis of the vasa vasorum and adventitium were seen ……..it is the initial injury to the vasa vasorum that defines post-XRT vasculopathy and that distinguishes it from spontaneous atheromatous disease

…. HNXRT and NXRT do appear to at least double the RR of TIA or stroke; the adjuvant NXRT for breast cancer, where carotid XRT exposure is usually

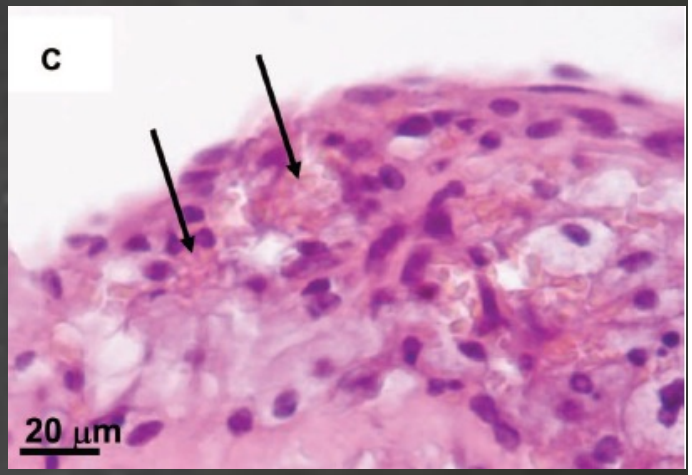
l' irradiazione di arterie di animali da esperimento ipercolesterolemici esita in un processo aterosclerotico accelerato

Placche "Radiation related" sono ricche di macrofagi a contenuto lipidico (foam cells)

Placche "age related" ricche di collagene con minima infiltrazione di macrofagi

Ionizing Radiation Accelerates the Development of Atherosclerotic Lesions in ApoE$^{-/-}$ Mice and Predisposes to an Inflammatory Plaque Phenotype Prone to Hemorrhage

quality of the plaque was markedly influenced by irradiation. There were significant increases in the number of lesions characterized by macrophage-rich cores, low collagen content, and intraplaque hemorrhage in irradiated arteries. This finding is of particular interest in the light of recent findings of an association between plaque hemorrhage, cholesterol accumulation, and macrophage infiltration.[21] Kolodgie et al[21] concluded that intraplaque hemorrhage provided a powerful atherogenic stimulus and was a critical event in the induction of plaque instability and rupture in human atherosclerotic lesions.



American Journal of Pathology, Vol. 168, No. 2, February 2006

Huang et al. Radiation Oncology 2013, 8:261
http://www.ro-journal.com/content/8/1/261

RADIATION ONCOLOGY

RESEARCH Open Access

Long-term effects on carotid intima-media thickness after radiotherapy in patients with nasopharyngeal carcinoma

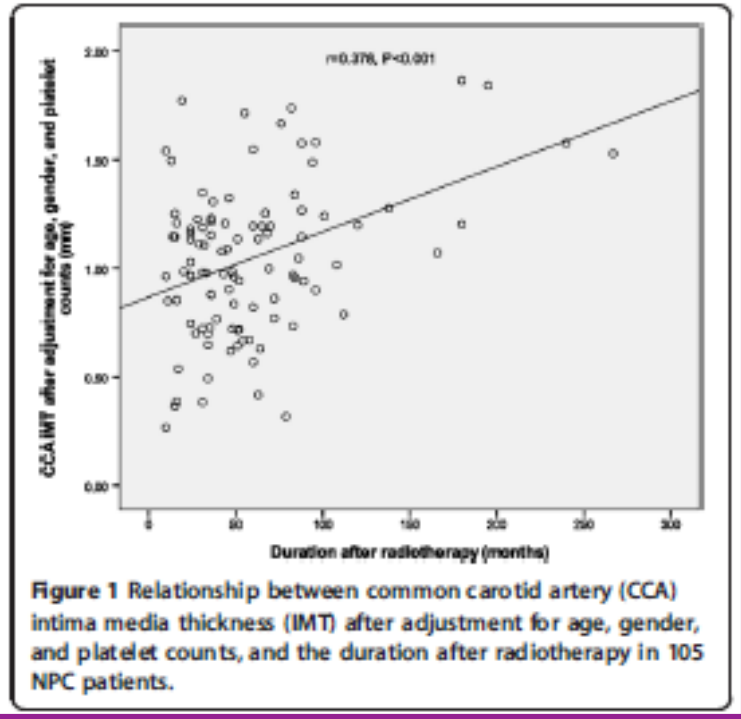


Figure 1 Relationship between common carotid artery (CCA) intima media thickness (IMT) after adjustment for age, gender, and platelet counts, and the duration after radiotherapy in 105 NPC patients.

Table 3 Correlation analysis of the effects of candidate risk factors on CCA IMT in NPC patients

Variables	*Correlation coefficient*	*P value*
Age	*0.598*	*<0.001*
Duration of radiotherapy therapy (months)	*0.615*	*<0.001*
hs-CRP	*0.222*	*0.014*
Glucose, mg/dL	*0.147*	*0.144*
HBA1c	*0.200*	*0.049*
Total Cholesterol	*−0.074*	*0.459*
HDL	*−0.030*	*0.765*
LDL-C	*0.013*	*0.895*
Body mass index	*0.045*	*0.652*
Platelet count	*0.326*	*0.001*

Conclusioni……radiation-induced vasculopathy is a dynamic and progressive process from the late radiation effects. . .

. . . after adjustment for age, gender and platelet count, IMT increased in a linear manner with duration after radiotherapy

nato 1951

All' età di 53 anni (2004) :

- Agosto 2004 sindrome coronarica acuta NSTEMI in malattia coronarica plurivasale

  PCI con DES su ramo intermedio
  PCI con DES su coronaria destra prossimale
  PCI con DES su coronaria discendente anteriore t. medio

- Gennaio 2005 test ergometrico positivo :

  restenosi intrastent su Dx ostiale > POBA su coronaria destra ostiale
  stenosi "de novo" tratto medio coronaria DX >PCI con STENT

- Maggio 2005 controllo elettivo

  Restenosi intrastent su Dx ostiale >re PTCA con impianto di DES

. 2014 . . . . . .

frontiers in ONCOLOGY

REVIEW ARTICLE
published: 18 February 2015
doi: 10.3389/fonc.2015.00039

Radiation-induced heart disease: pathologic abnormalities and putative mechanisms

CORONARY ARTERY DISEASE

The initiation of RIHD in the coronary arteries is similar to that of most other tissues as radiation leads to microvascular damage, inflammation, and subsequent fibrosis.

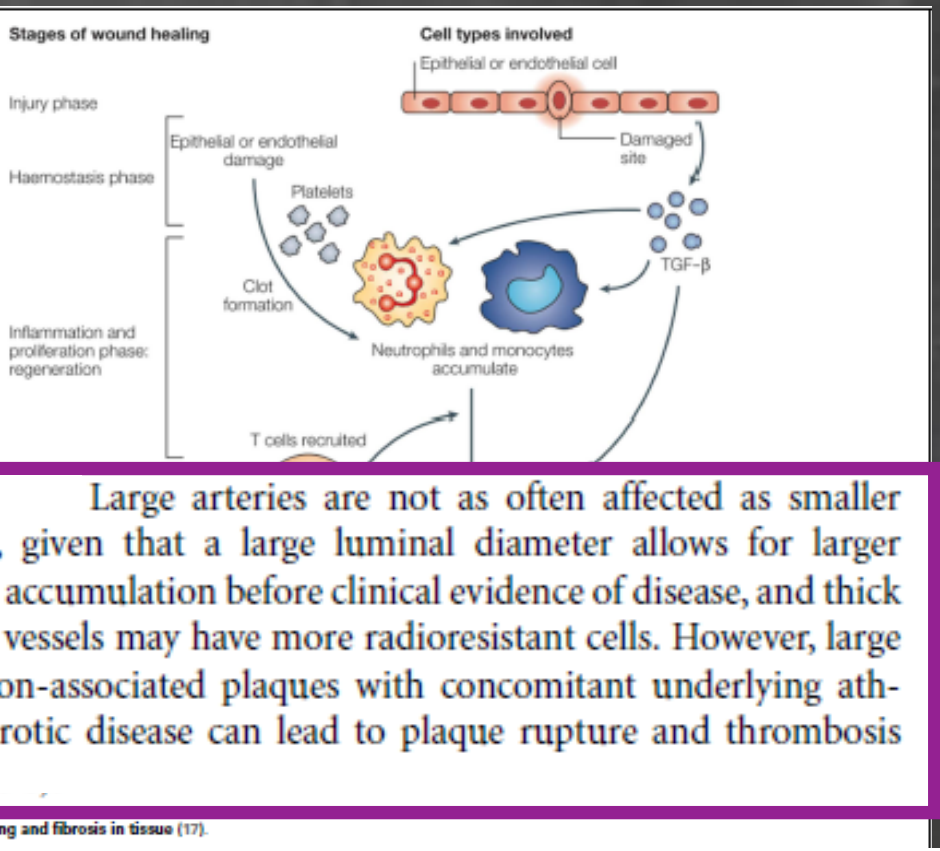


FIGURE 1 | Wound healing and fibrosis in tissue (17).

Large arteries are not as often affected as smaller vessels, given that a large luminal diameter allows for larger plaque accumulation before clinical evidence of disease, and thick walled vessels may have more radioresistant cells. However, large radiation-associated plaques with concomitant underlying atherosclerotic disease can lead to plaque rupture and thrombosis

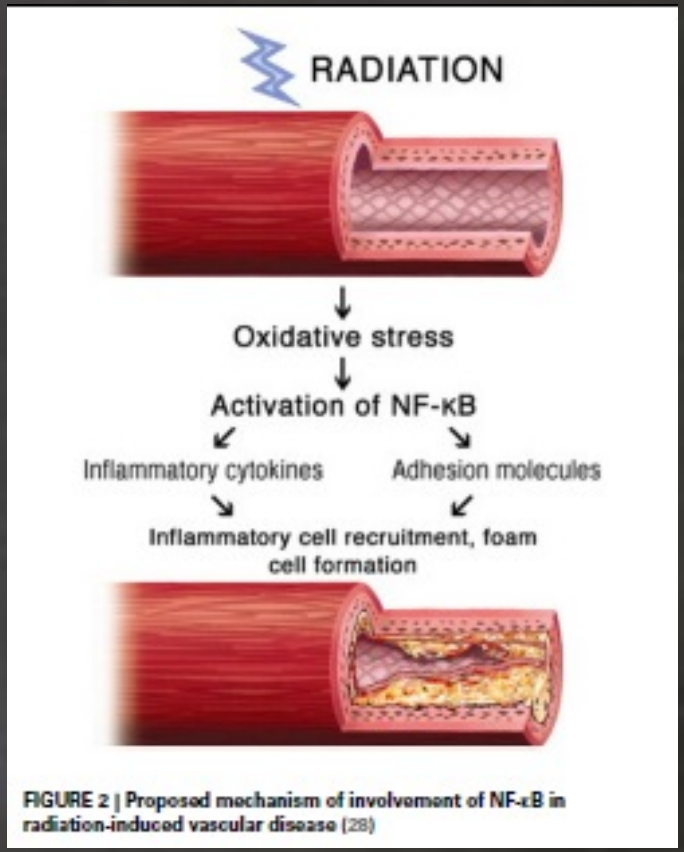
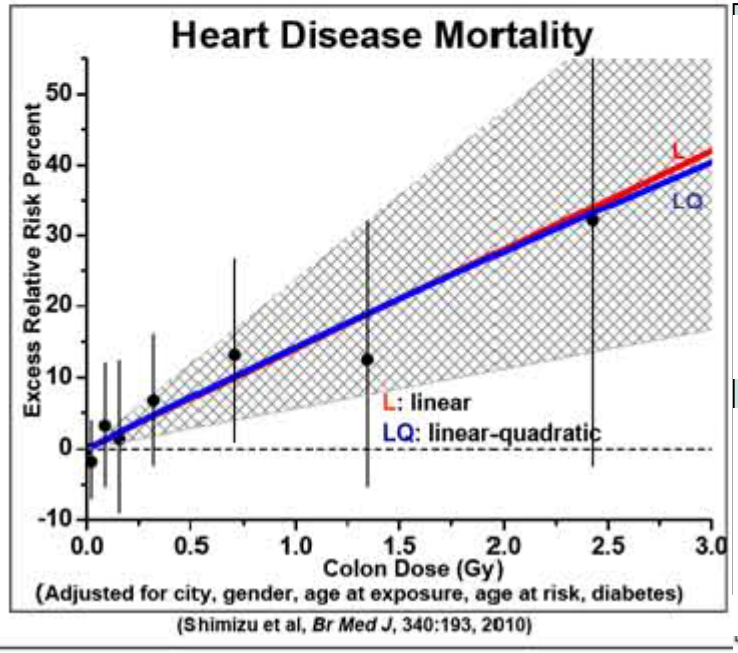


FIGURE 2 | Proposed mechanism of involvement of NF-κB in radiation-induced vascular disease (28)

. . . doses above 0.5 Gy of radiation exposure are associated with an elevated risk of both stroke and heart disease, and these findings are supported by a variety of clinical and laboratory data showing that various circulatory disease risk factors are also associated with radiation dose. There is uncertainty in the degree of risk at lower doses (Shimizu et al., 2010).

- **Clear evidence of heart disease risk at doses *below* 4-5 Gy (previous assumed "dose-effect threshold" level)**
- **Dose-response for heart disease mortality appears linear, but risk is uncertain below about 0.5 Gy.**



(Shimizu et al, *Br Med J*, 340:193, 2010)

Dose of RT ≥8 Gy are associated with increased size and number of these lesions in the major arteries. In addition, the plaques that result may be more unstable and macrophage-laden (34). Unlike stable collagenous plaques, radiation-related plaques tend to grow, rupture, and lead to a myocardial infarction or cerebrovascular accident more often

The endothelial cells respond with inflammatory markers and adhesion molecules to recruit peripheral leukocytes with doses as little as ≥2 Gy.

Medastinal radiation > 15 Gy is a reasonable risk factor for the development of CAD

Orzan F et Al

Br Heart J 1993;69:496–500

Severe coronary artery disease after radiation therapy of the chest and mediastinum: clinical presentation and treatment

Table 1 *Data on 15 patients with coronary artery disease after radiotherapy*

Patient No	*Age (yr)*	*Sex*	*CRF*	*Latency (yr)*	*Dose (Gy)*	*Neoplasm*
1	49	M	—	28	122	Hodgkin
2	46	F	—	23	100	Hodgkin
3	39	F	—	15	92	Lymphoma
4	56	F	—	4	42	Breast cancer
5	49	F	—	11	40	Breast cancer
6	52	M	—	10	42	Seminoma
7	51	F	—	3	40	Breast cancer
8	56	F	Chol	6	45	Breast cancer
9	41	M	—	13	42	Hodgkin
10	40	M	—	12	45	Hodgkin
11	43	M	Smoke	13	100	Hodgkin
12	32	M	—	14	40	Hodgkin
13	51	F	—	4	42	Breast cancer
14	25	F	—	10	41	Hodgkin
15	31	M	—	15	46	Hodgkin

Chol, hypercholesterolaemia; CRF, coronary risk factors.

***Conclusions*—Coronary arterial disease can be reasonably ascribed to the effects of chest irradiation when the patients are young and free from risk factors, especially if the obstructions are ostial and there is important damage to other cardiac structures.**

Table 1 – Excess risks of cardiac mortality after Hodgkin lymphoma therapy over time.

	Stanford Hoppe et al. [82] (1997)		Harvard Ng et al. [83] (2002)		The Netherlands Aleman et al. [84] (2003)		BNLI* Swerdlow et al. [11] (2007)		CCSS Castellino et al. [10] (2011)
Median age in years (range)	Not reported		25 (3–50)		25.7 (2–40)		Approximately 30 years (all ages)		14 (2–20)
Interval (years)	RR	AER	RR	AER	RR	AER	RR	AER	AER
0–5	2	6.4	4.4	6.3	7.6	6.1			
5–10	3.6	20.1	2.7	5.3	7.0	10.6			
10–15	3.0	20.5	2.5	7.2	4.5	10.7			
15–20	5.0	54.2	2.8	13.9	6.8	28.7			
>20	5.6	70.6	4.5	41.1	8.3	53.9			

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

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

The NEW ENGLAND JOURNAL of MEDICINE

MARCH 14, 2013

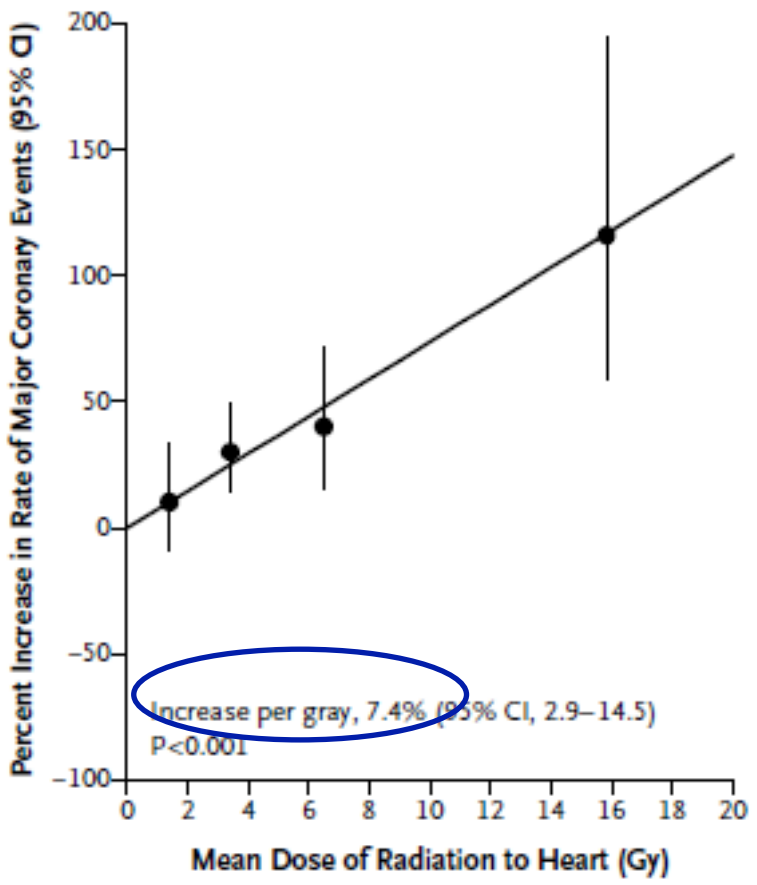


Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Overview on cardiac, pulmonary and cutaneous toxicity in patients treated with adjuvant radiotherapy for breast cancer

In left BC patients, both in post-mastectomy as in BCS setting, the most commonly affected vessel is the left anterior descendent coronary artery (LADCA). CAD rate increased linearly with the mean dose to the heart, with no apparent threshold.

Accelerated partial breast irradiation (APBI) and intra-operative RT (IORT) techniques may minimize RT dose to the coronary arteries [20]. A reduced heart dose could be obtained using prone position setup [21, 22]. Intensity modulated radiation therapy (IMRT) and respiratory gating should be further studied to reduce RT dose to the coronary arteries [23].

Concomitant administration of cardio-toxic systemic treatments should be strongly considered. Cardiotoxicity of anthracycline-based chemotherapy regimens is well-known and studied; therefore concomitant use with RT is not recommended.

Received: 16 February 2016 / Accepted: 20 March 2016

Screening for Coronary Artery Disease After Mediastinal Irradiation for Hodgkin's Disease

VOLUME 25 · NUMBER 1 · JANUARY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

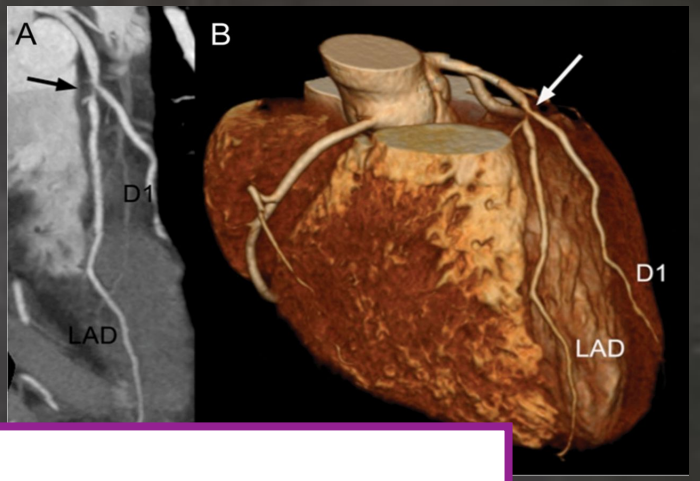


Table 3. Angiography Results

Result	All Patients (n = 40)		Years After Irradiation: 2-10 (n = 5)		11-20 (n = 19)		> 20 (n = 16)	
	No.	%	No.	%	No.	%	No.	%
Coronary disease ≥ 50%	22	55	2	40	11	58	9	56
Coronary disease ≥ 70%	16	40	1	20	9	47	6	38
Left main or three-vessel disease	8	20	0	0	6	32	2	13
Two-vessel disease	4	10	0	0	2	11	2	13
One-vessel disease	4	10	1	20	1	5	2	13

Table 6. Mortality From Acute Myocardial Infarction Among 972 Patients Treated for Hodgkin's Disease

Patient Group	No. at Risk	Observed/Expected Events	Relative Risk	95% CI	Absolute Risk*
All patients†	972	33 of 4.39	7.5	5.0 to 10.1	22.9
Males	531	28 of 3.43	8.2	5.1 to 11.2	36.4
Females	441	5 of 0.96	5.2	1.7 to 12.1	7.1
Within 10 years of irradiation	972	14 of 1.91	7.3	4.0 to 10.5	15.6
10 through 19 years after irradiation	565	13 of 1.61	8.1	4.3 to 12.4	30.3
> 20 years after irradiation	213	6 of 0.87	6.9	2.5 to 15.1	53.0

*Excess deaths per 10,000 person-years of observation.
†Patients treated at Stanford University Medical Center with ≥ 35 Gy to the mediastinum who resided in Northern California.

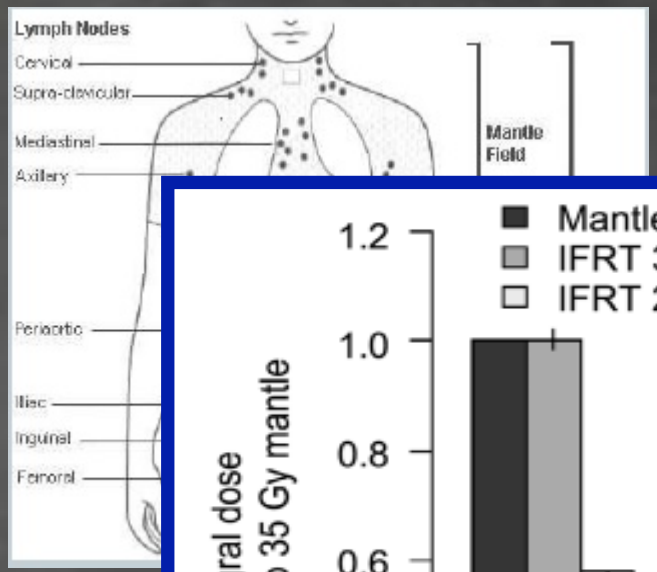
Radiation Oncology

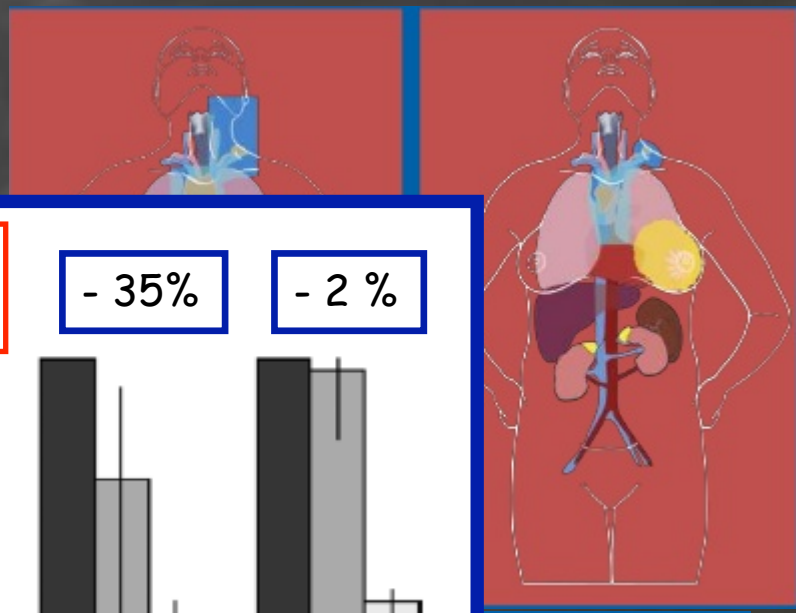
BioMed Central

Research

Open Access

A comparison of mantle versus involved-field radiotherapy for Hodgkin's lymphoma: reduction in normal tissue dose and second cancer risk





2008 – Involved Node Radiotherapy (INRT)

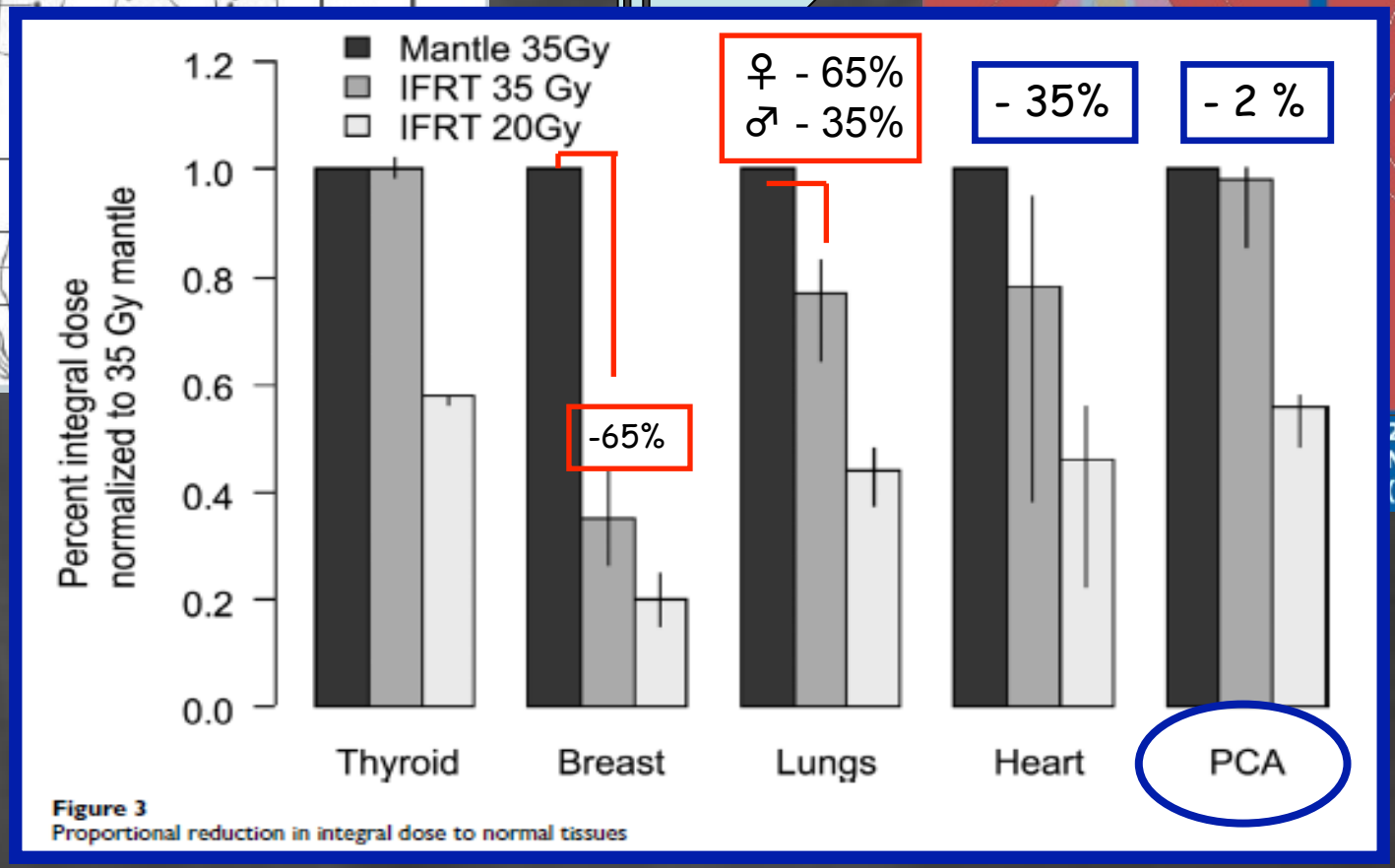
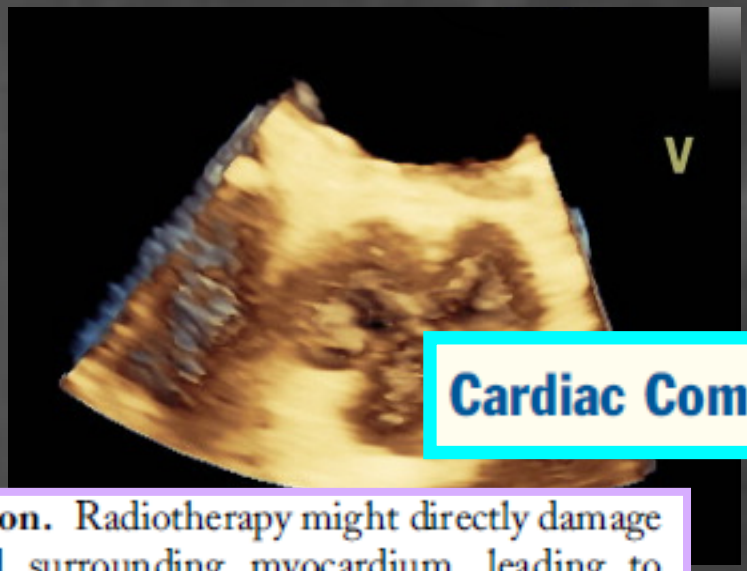


Figure 3
Proportional reduction in integral dose to normal tissues

nato 1951

. . . 2014 comparsa di ANGINA PECTORIS > coronarografia:

buon esito delle precedenti rivascolarizzazioni



ETT:

FE v sx 40%
DP max 30 mmHg
Dp med 21 mmHg

ETE:

DP med 29 mmHg

(J Am Coll Cardiol 2013;61:2319-28

Cardiac Complications of Thoracic Irradiation

Valvular dysfunction. Radiotherapy might directly damage cardiac valves and surrounding myocardium, leading to fibrotic thickening, valvular retraction, and late calcification (5). The incidence of valvular dysfunction has been reported to increase during the second decade after mediastinal radiotherapy for HD

RIG

IVO

The valves were found to be thicker with reduced leaflet motion and calcification (5). These results suggest that valve retraction is the predominant early change that causes regurgitation and that it might take in excess of 20 years for the valves to become significantly thickened, calcified, and stenotic.

Angio TC torace addome:

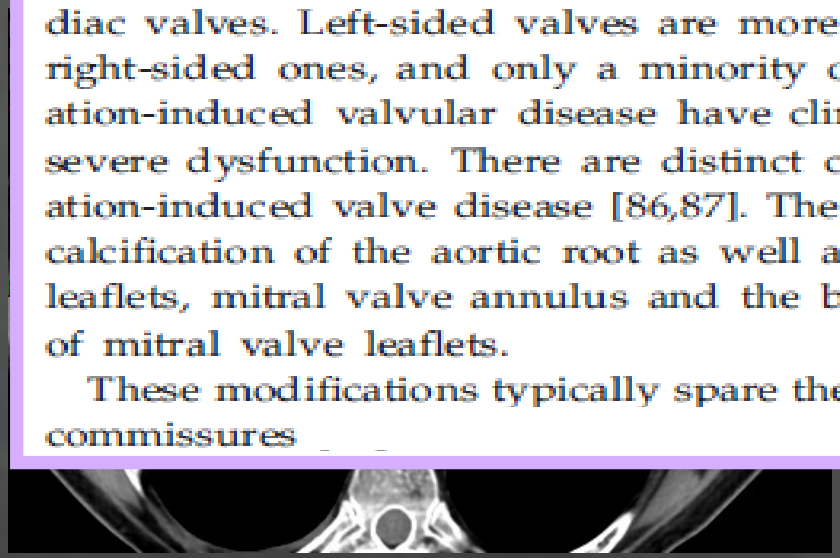
. . . Si riconoscono grossolane **calcificazioni parietali del tratto ascendente dell'aorta toracica** e calcificazioni di minore entità sono apprezzabili all'arco . . . . .si segnalano estese e **grossolane calcificazioni valvolari e coronariche** . . .

. . .grave aterosclerosi dell'aorta addominale ... Grossolane calcificazioni si osservano a livello degli assi arteriosi iliaco femorali e delle arterie iliache comuni . . .

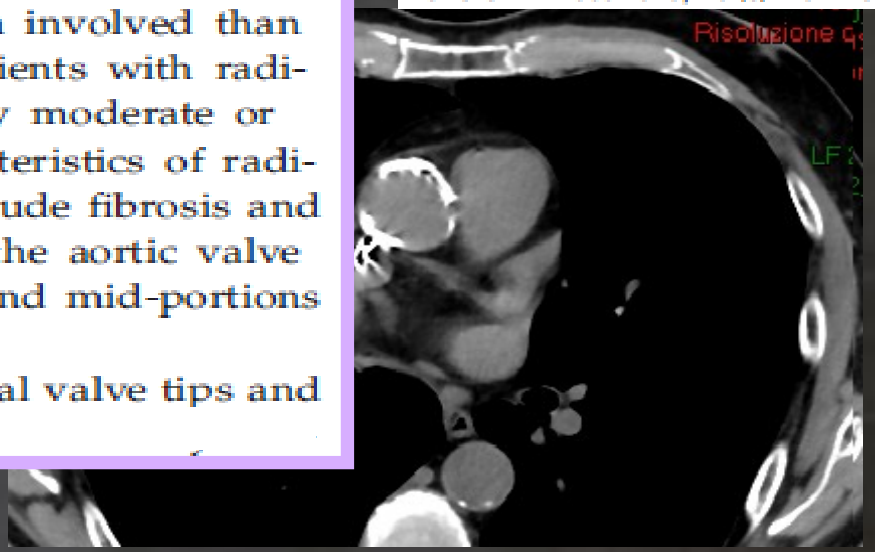
Update on cardiotoxicity of anti-cancer treatments

Valvular heart disease is common after radiation because radiation causes fibrous thickening of cardiac valves. Left-sided valves are more often involved than right-sided ones, and only a minority of patients with radiation-induced valvular disease have clinically moderate or severe dysfunction. There are distinct characteristics of radiation-induced valve disease [86,87]. They include fibrosis and calcification of the aortic root as well as of the aortic valve leaflets, mitral valve annulus and the base and mid-portions of mitral valve leaflets.

These modifications typically spare the mitral valve tips and commissures



Eur J Clin Invest 2016; 46 (3): 264–284



nato 1951

. . . .

- Marzo 2007: riscontro ECGgrafico di BBS alternato a BBD con comparsa di BAV 2:1 all' incremento di FC > indicazione ad impianto PM DDD complicato da arresto cardiaco intraprocedurale risolto con ACLS ; al termine della procedura documentata la TOTALE PM DIPENDENZA del paziente

Cardiac Complications of Thoracic Irradiation

(J Am Coll Cardiol 2013;61:2319–28

Conduction system. Abnormalities along the entire conduction system have been described in the setting of radiotherapy, including varying degrees of atrioventricular block, sick sinus syndrome, prolonged QTc, supraventricular arrhythmias, and ventricular tachycardia (53,58). Right bundle branch block is more commonly observed than left bundle branch block post-RT, likely due to higher radiation exposure of the right ventricle due to its anterior location.

nato 1951

. . .

2008 asportazione endoscopica di polipo intestinale cancerizzato del sigma distale

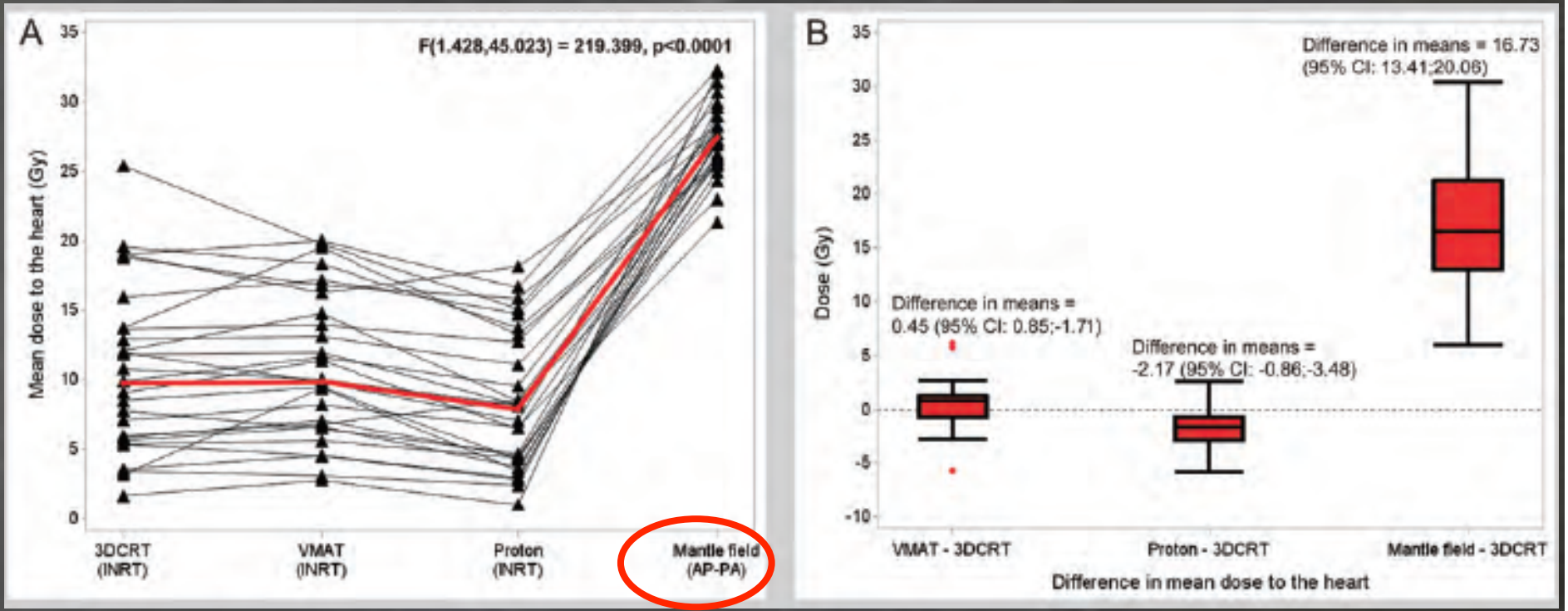
- 2008 intervento chirurgico di resezione del sigma per neoplasia intestinale pN1 con secondarismi linfonodali

  successivo trattamento chemioterapico con 3 cicli di CAPECITABINA interrotto per neuropatia periferica

- 2010 asportazione endoscopica di polipo iperplastico (adenoma) colon discendente

. . .

Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma



In conclusion, highly conformal radiotherapy significantly lowers the dose to the heart, lungs, and breasts and provides lower estimated risks of late effects compared with Mantle Field (MF) treatment.

Annals of Oncology 24: 2113–2118, 2013

nato 1951

. . . .

febbraio 2016:

ricovero per scompenso cardiaco NYHA III con versamento pleurico sx massivo ed atelettasia polmonare , sottoposto a ripetute toracentesi . .

. . . . Ad ecocardio:

peggioramento della già nota STENOSI MITRALICA e della FE v sx

(Dp mitralico medio 14 mmHg vs 9 mmHg post TAVI

FE 45% vs 54% post TAVI)

. . . . CITOLOGIA su liquido pleurico negativa per cellule neoplastiche

. . . .


PROS
&
CONS

Cancer Survivors: A Booming Population

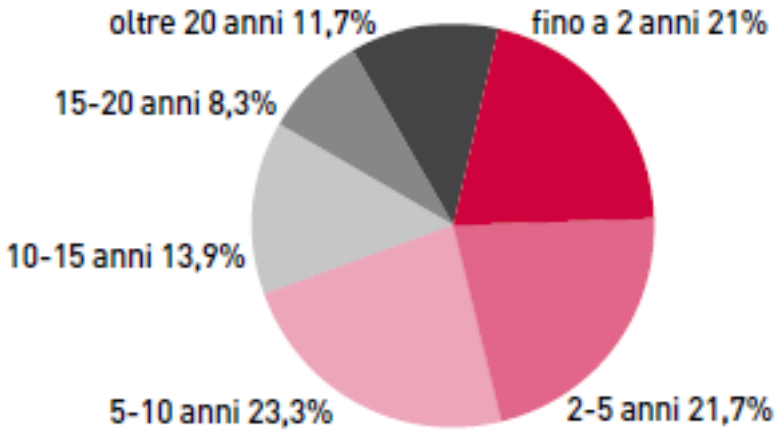
Carla Parry[1], Erin E. Kent[1,2], Angela B. Mariotto[3], Catherine M. Alfano[1], and Julia H. Rowland[1]

Cancer Epidemiol Biomarkers Prev; 20(10); 1996–2005. 2011

Miglior sopravvivenza

Invecchiamento della popolazione

Trend in costante incremento dei pazienti oncologici “prevalenti”



Tutti i tumori*	%	Pazienti in vita
Tempo trascorso dalla diagnosi		
fino a 2 anni	21,0%	471.303
da 2 a 5 anni	21,7%	486.969
da 5 a 10 anni	23,3%	523.553
da 10 a 15 anni	13,9%	312.823
da 15 a 20 anni	8,3%	186.704
oltre 20 anni	11,7%	262.600

*eccetto tumori cutanei non melanomatosi

Il 57% dei casi (2.2% della popolazione italiana) è costituito dai cosiddetti **lungo sopravviventi**, con diagnosi di tumore ≥ 5 anni

Sede tumorale	Maschi ♂		Femmine ♀	
	Probabilità di sopravvivere altri 5 anni essendo sopravvissuto il 1° anno dalla diagnosi	Probabilità di sopravvivere altri 5 anni essendo sopravvissuto i primi 5 anni dalla diagnosi	Probabilità di sopravvivere altri 5 anni essendo sopravvissuto il 1° anno dalla diagnosi	Probabilità di sopravvivere altri 5 anni essendo sopravvissuto i primi 5 anni dalla diagnosi
Vie aerodigestive superiori	66	80	71	86
Esofago	32	95	39	92
Stomaco	57	86	58	89
Colon-retto	74	91	74	92
Colon	75	93	76	94
Retto	72	88	69	88
Utero corpo			82	92
Ovaio			50	80
Linfoma di Hodgkin	85	93	91	95
Linfomi non-Hodgkin	78	85	82	86
Mieloma	54	62	56	65
Leucemie	65	75	67	81
Tutti i tumori, esclusi carcinomi della cute	73	87	77	89

Chi sopravvive 5 anni ha per molte sedi tumorali (testicolo, corpo dell'utero, ma anche melanoma, linfomi di Hodgkin e in misura minore tumore del colon-retto) prospettive di sopravvivenza che si avvicinano a quelle della popolazione generale, che non ha avuto una neoplasia. Per il tumore della mammella femminile, nonostante sia un tumore complessivamente a buona prognosi, è presente una quota di ulteriore mortalità che si riduce molto lentamente nel tempo.

. Long-term survivors are at increased risk to develop treatment-induced side effects, such as radiogenic second cancer, complications of the cardiovascular (10, 11) and central nervous (12, 13) systems, fertility problems (14), and myriad other toxicities (15).

RECOMMENDATIONS

Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography

ng (2013) 14, 721–740

Risk Factors for Radiation-Induced Cardiotoxicity

Total dose >30–35 Gy
Higher dose/fraction >2 Gy/day
Field size (volume of heart irradiated)
Relative field weighting (anterior/posterior positioning)
Presence of tumor next to the heart
Younger age at exposure
Time since exposure
Type of radiation source (cobalt)
Cardiotoxic chemotherapy (e.g., anthracycline)
Other cardiovascular risk factors (e.g., diabetes, smoking)
Technique (reduced with CT plan)

Adapted, with permission, from Gaya et al. (16) and Carver et al. (20).
CT = computed tomography.

J Am Coll Cardiol 2013;61:2319–28

Table I Rel

Types
RIHD
Ischaemic heart disease
Cardiac death

The reported relati
exposure.

diac Mortality in
s

w et al. (2)		Castellino et al. (10)
AR	RR	AR
4.6	—	—
10.9	5.1	—
8.5	12.3	—
28.9	12.3	—
22.2	25.0	—

High-risk patients definition: anterior or left-side chest irradiation with ≥1 risk factors for RIHD.

RECOMMENDATIONS

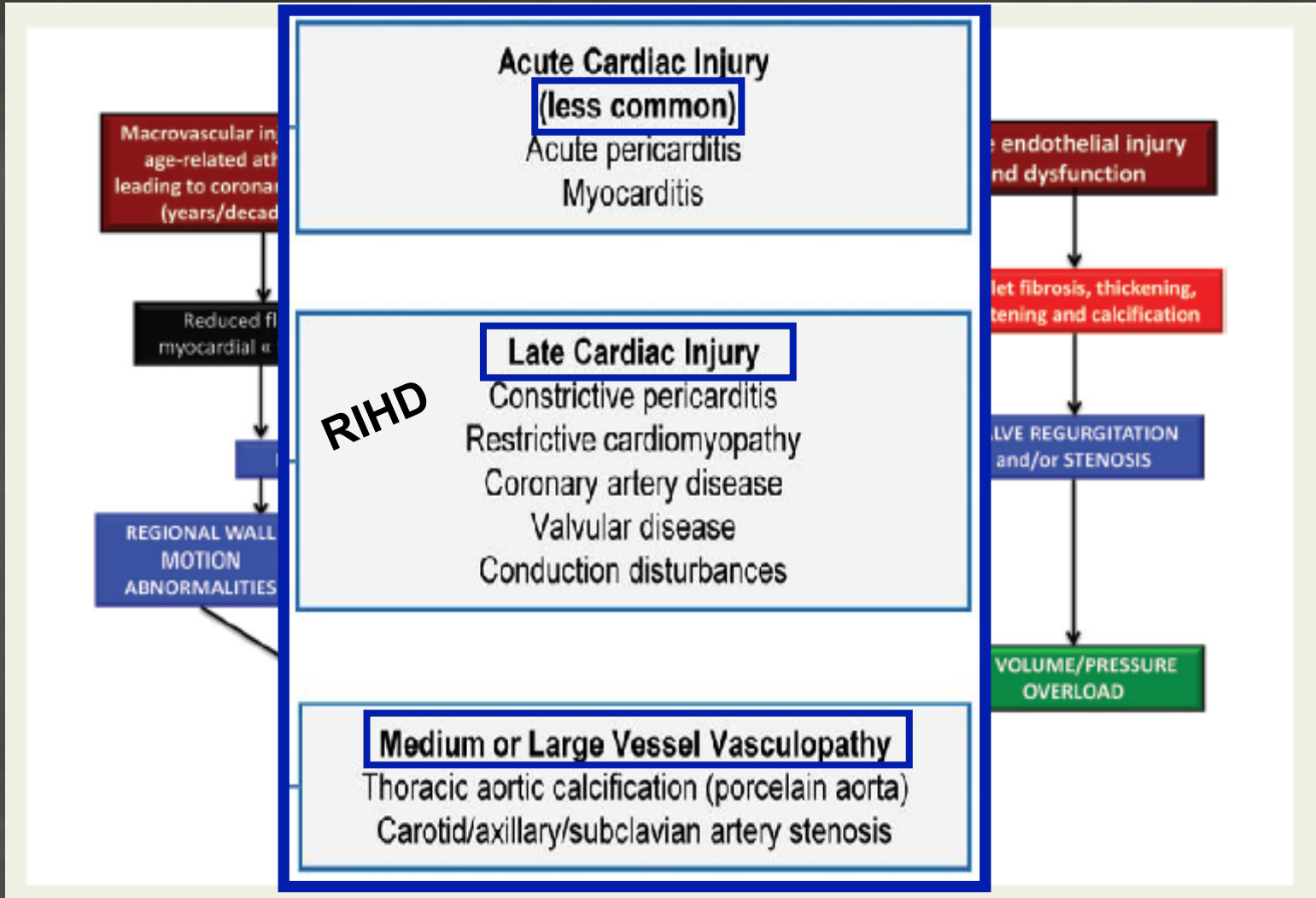


Figure 1 Pathophysiological manifestations of radiation-induced heart disease for different radiosensitive structures within the heart. LV: left ventricle; RT: radiotherapy.

RECOMMENDATIONS

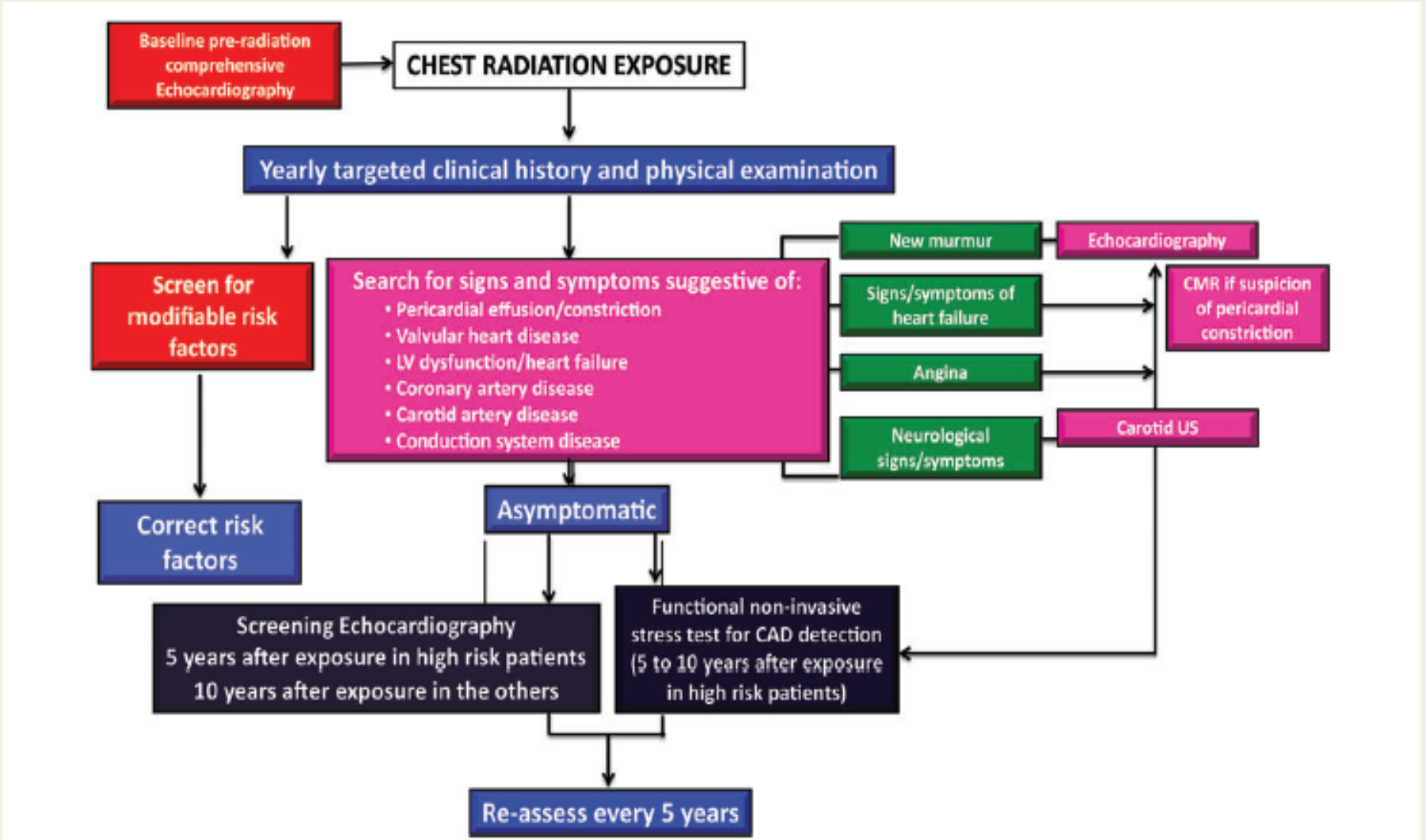


Figure 10 Algorithm for patient management after chest radiotherapy. LV: left ventricle; US: ultrasound. High-risk patients: refer to *Table 1*. Modifiable risk factors refer to: hypertension, tobacco use, hypercholesterolaemia, obesity, and diabetes.

La radioterapia

La radioterapia è quella *branca della medicina specialistica* che impiega le radiazioni per produrre un *effetto radiobiologico distruttivo* sul tessuto neoplastico.

D.Lgs. 187/2000

Attuazione della direttiva 97/43 EURATOM

Obiettivo principale:

riuscire a somministrare il massimo di dose al volume bersaglio (neoplasia) ..

..e nel contempo **salvaguardare** i tessuti sani circostanti.

There is compelling evidence
risk of heart disease. Althoug
likely to reduce the prevalen
of RIHD is expected to increase in cancer survivors who have received old radiotherapy regimens. Improved knowledge of the prevalence of

. The adequate strategy for screening of RIHD remains a source of debate in the radiation and medical oncology community. Large prospective studies are required to confirm the clinical utility of non-invasive imaging for comprehensive screening and surveillance of asymptomatic cancer survivors. This will enable targeted follow-up, screening, and intervention.


"Follia
è fare sempre
la stessa cosa
aspettandosi
risultati diversi"
Albert Einstein