FONDAZIONE SALVATORE MAUGERI
CLINICA DEL LAVORO E DELLA RIABILITAZIONE
I.R.C.C.S.

Danni cardiaci da radioterapia: problema attuale o ricordo di un'epoca passata?

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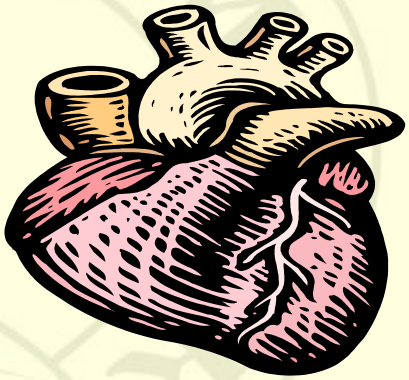
Il cuore è un organo radioresistente:



E' però ormai accertato che l'irradiazione completa o parziale del cuore può provocare un ampio spettro di malattie cardiovascolari

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Main conditions for radiation-related heart disease

Pericarditis

Pericardial fibrosis

Valvular disease

Myocardial fibrosis

Coronary artery Disease

(chronic ischemia
angina pectoris
myocardial infarction)

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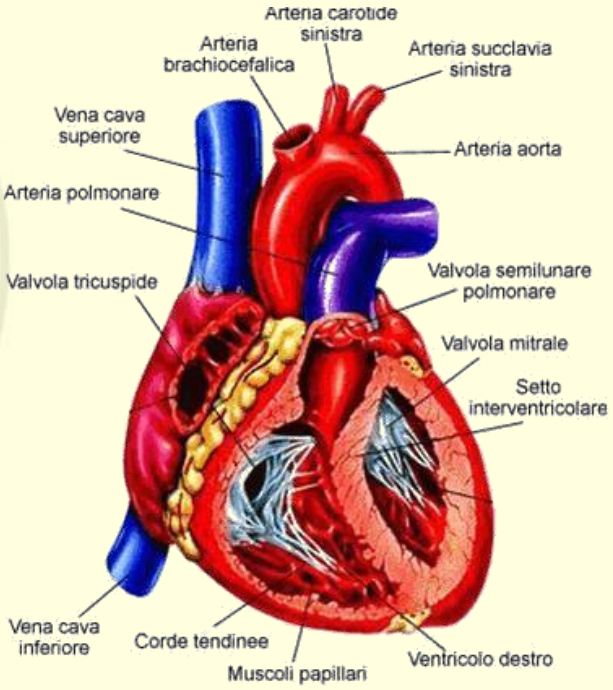
RT e Tossicità cardiovascolare

- **Miocardio**
  - Fibrosi interstiziale diffusa
  - Ischemia del microcircolo
  - Alterazioni della conduzione
- **Pericardio**
  - Danno vascolare e aumentata permeabilità
  - Essudato / Ispessimento pericardico
- **Valvole**
  - Fibrosi a eziologia ignota
- **Coronarie**
  - Restringimento prossimale dei vasi con riduzione della muscolare media e ispessimento fibrotico
  - Iperplasia intimale, trombi, deposito lipidico



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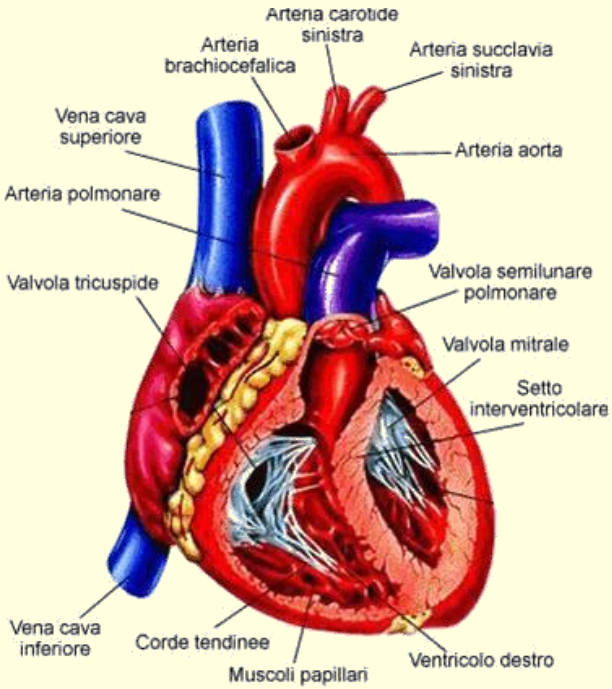
RT e Tossicità cardiovascolare

1. Radiation-induced pericarditis may occur if a large proportion of the heart (>30%) receives a dose of >50 Gy. The mean latency is approximately 1 year
2. Radiation-induced myocardial damage may be diagnosed at lower mean doses to the heart. The mean latency is >5 years
3. The risk of radiation-induced cardiovascular disease begins to increase 10 years after irradiation and is progressive with time. A significant increase of risk
of cardiovascular disease has been observed after mean heart doses lower than 10% of the generally accepted tolerance dose to the heart of 40–50 Gy fractionated exposure



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RT e Tossicità cardiovascolare

- **Rutqvist** et al. IJROBP '92
  - ≈ *960 pz. (1971-76) Trattamento radiante sulla parete toracica + linfonodi loco-regionali*
  - ≈ Rischio di morte per tossicità cardiaca aumentato di 3 volte nei soggetti con maggiore volume irradiato rispetto ai controlli
- **Gyenes** et al. Rad Oncol '98
  - ≈ Persistenza del rischio nel tempo rispetto ai controlli
  - ≈ Incremento del rischio di decessi cardiaci di 2 volte (2.5 volte per rischio di infarto miocardico)

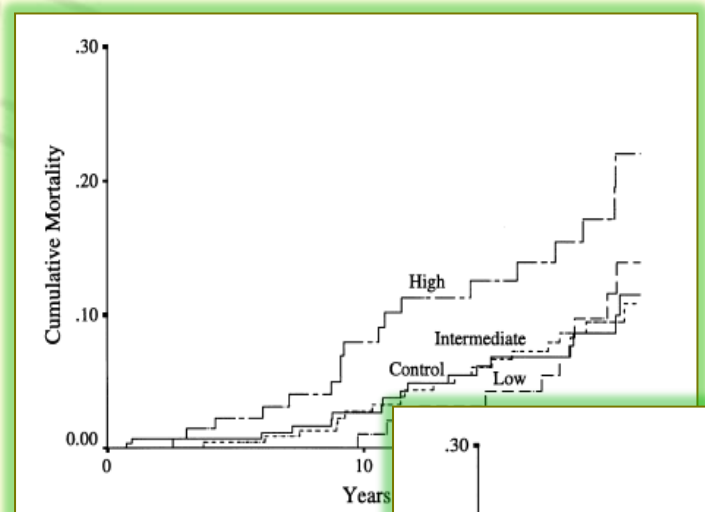

Fig. 2. Cumulative cardiovascular mortalit
subgroups according to cardiac dose-volu

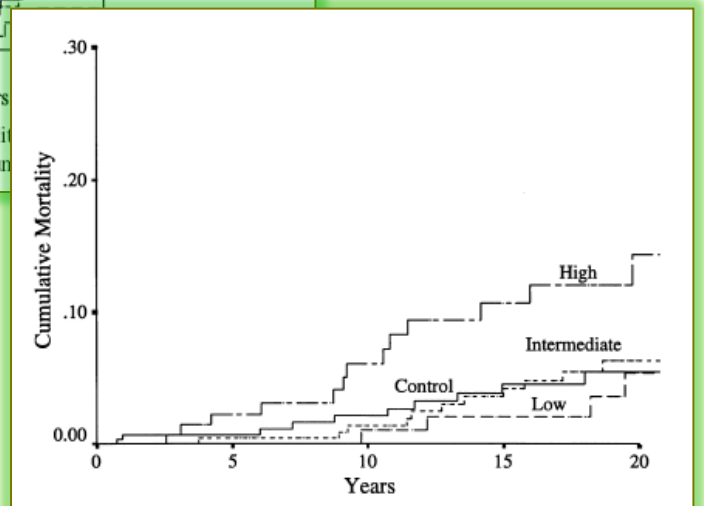

Fig. 3. Cumulative mortality rates due to ischemic heart disease in the different patient subgroups according to cardiac dose-volumes.

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RT e Tossicità cardiovascolare

- **Rutqvist** '90; **Cuzick** '94; **EBCTCG** '95; **Paszat** '98

  ≈ Incremento del rischio di cardiotossicità con RT post-mastectomia

  ≈ Riduzione della mortalità legata alla malattia, ma incremento di quella cardiaca

- **NSABP-06** '95; **DBCCG** '99; **Whelan** '00

  ≈ Studi con tecniche di irradiazione più recenti evidenziano una riduzione della mortalità

- **Nixon** '98; **Gagliardi** '01

  ≈ Irradiazione dopo chirurgia conservativa: tossicità sensibilmente inferiore
  (*Vol. ventricolo sinistro irradiato: 0-5%*)

- **Rutqvist** '98

  ≈ *684 pz. (1976-87) chir. conservativa + RT:* no differenze in rischio di IMA e morte per cardiotossicità rispetto a gruppo di controllo (*RR: 0.6 e 0.4, rispettivamente*)

Impatto dell'età, della lateralità della irradiazione e dei volumi di trattamento

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Background

Il danno cardiaco è stato soprattutto studiato in pazienti trattati per:

- **Linfoma di Hodgkin**
- **Carcinoma mammario**

PROGNOSI MIGLIORE → MAGGIORE FOLLOW-UP

- **Neoplasie polmonari, esofagee, timomi**
- **Irradiazione mediastinica per Seminoma**

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Conflicting and counfounding studies

Dose-volume

Orthovoltage energy

RT field

Patient age

Smoking

Comorbidities
Diabetes,
Hypertension

Fraction size

Length of Follow-up

Different techniques

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Conflicting and counfounding studies

Dose-volume

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RT field

Patient age

Comorbidities
Diabetes,
Hypertension

Smoking

Fraction size

Length of Follow-up

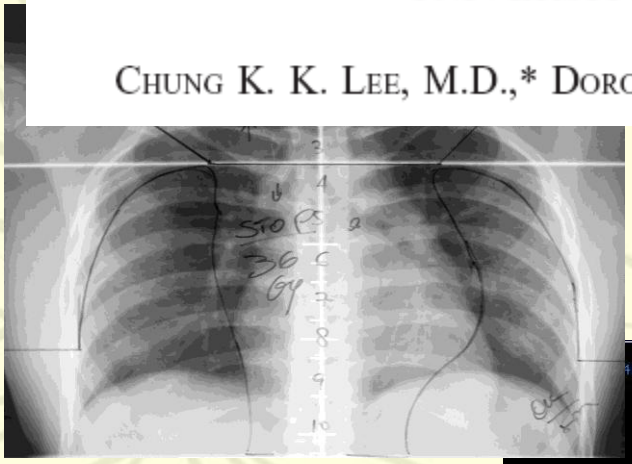
Different techniques

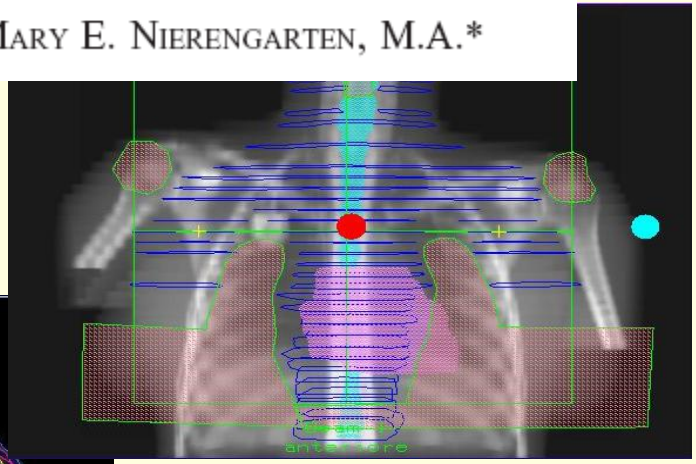
Linfoma di Hodgkin – Fattore età

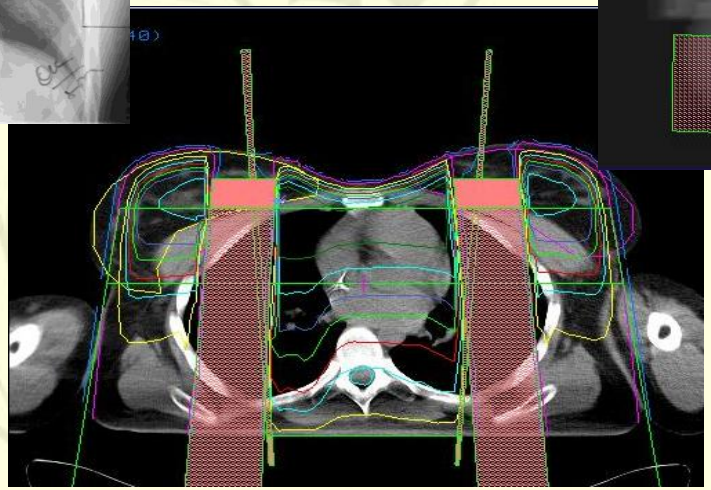
Relazione inversamente proporzionale tra l'età al trattamento ed il rischio di RIHD

THE NEED FOR LONG-TERM SURVEILLANCE FOR PATIENTS TREATED WITH CURATIVE RADIOTHERAPY FOR HODGKIN'S DISEASE: UNIVERSITY OF MINNESOTA EXPERIENCE

CHUNG K. K. LEE, M.D.,* DOROTHEE AEPPLI, PH.D.,† AND MARY E. NIERENGARTEN, M.A.*







By age, patients diagnosed at ≤18 years were 44 times more likely to die of a cardiovascular problem than the general population.

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Effetto dell'età al momento della RT sul rischio di IMA dopo trattamento per LH

Età	O/A	RR	95%CI
10-19	6	44.7	18.0-93.0
20-29	8	7.3	3.4-13.8
30-39	23	5.1	2.9-7.4
40-49	9	3.0	1.4-5.5
> 50	12	1.8	1.0-3.0

Hancock S., Stanford

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Conflicting and counfounding studies

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Diabetes,
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Fraction size

Length of Follow-up

Different techniques

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 4, pp. 980–987, 2009

0360-3016/09/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2008.11.016

CRITICAL REVIEW

RADIATION-INDUCED CARDIAC TOXICITY AFTER THERAPY FOR BREAST CANCER: INTERACTION BETWEEN TREATMENT ERA AND FOLLOW-UP DURATION

SENEM DEMIRCI, M.D.,*† JIHO NAM, M.D.,‡ JESSICA L. HUBBS, M.S.,‡ THU NGUYEN, B.A.,§ AND LAWRENCE B. MARKS, M.D.†‡

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Late cardiac mortality in 661 pts (1977-1994) med FU 12 years: increase at 20 years

Table 3. Cumulative Hazard Risk of Cardiac Death

	Right Sided		Left Sided	
Years After Radiation	%	95% CI	%	95% CI
5	0.09	0.03 to 2.4	0.09	0.03 to 2.4
10	1.5	0.07 to 3.4	1.9	0.09 to 3.9
15	2.9	1.4 to 5.8	4.4	2.5 to 7.5
20	3.6	1.8 to 7.2	6.4	3.5 to 11.5

Dalla 2° decade incremento della mortalità cardiaca

(Harris, 2006)

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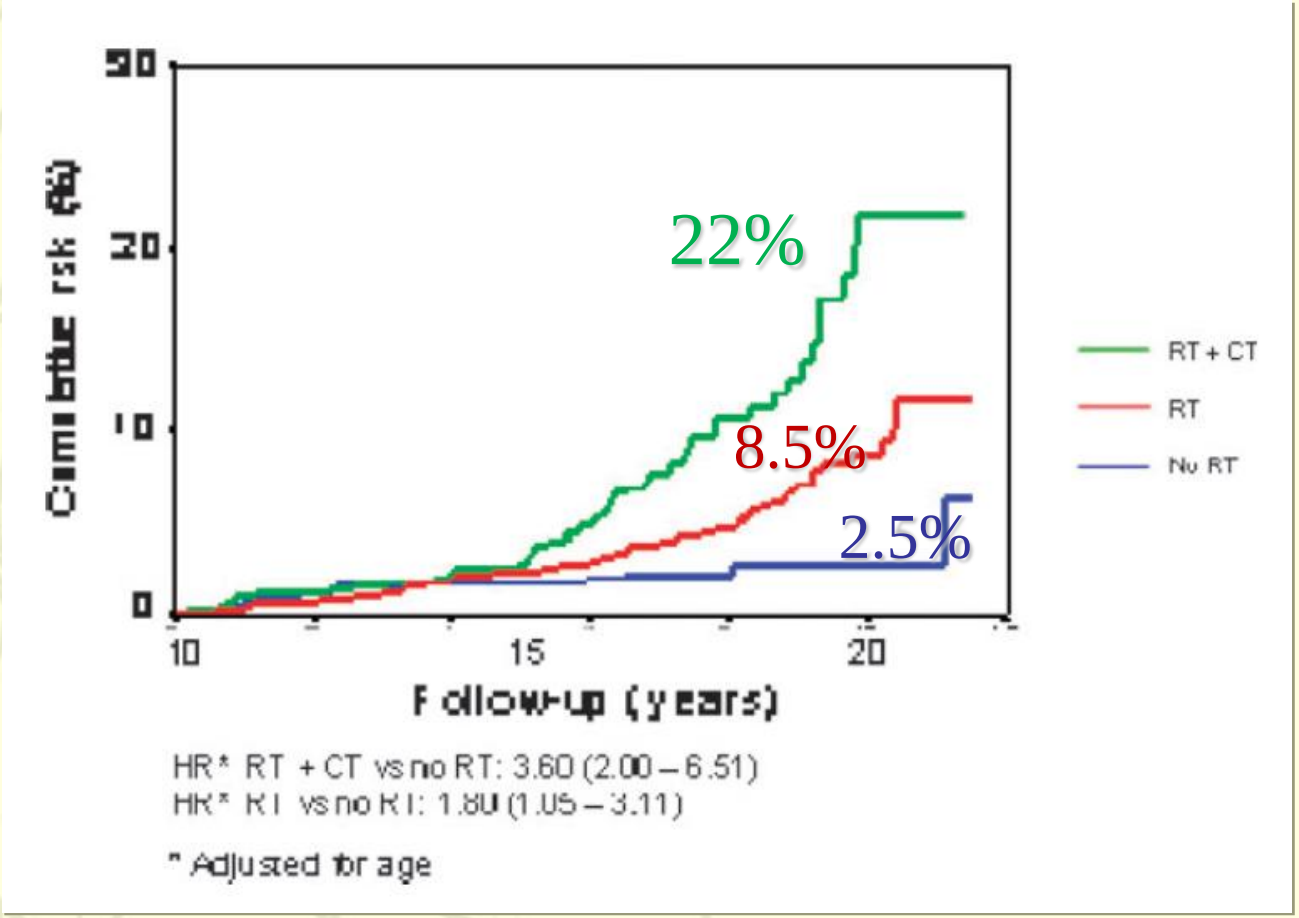
Rate of cardiac events 20 years after adjuvant treatment



(Hooning, 2007)

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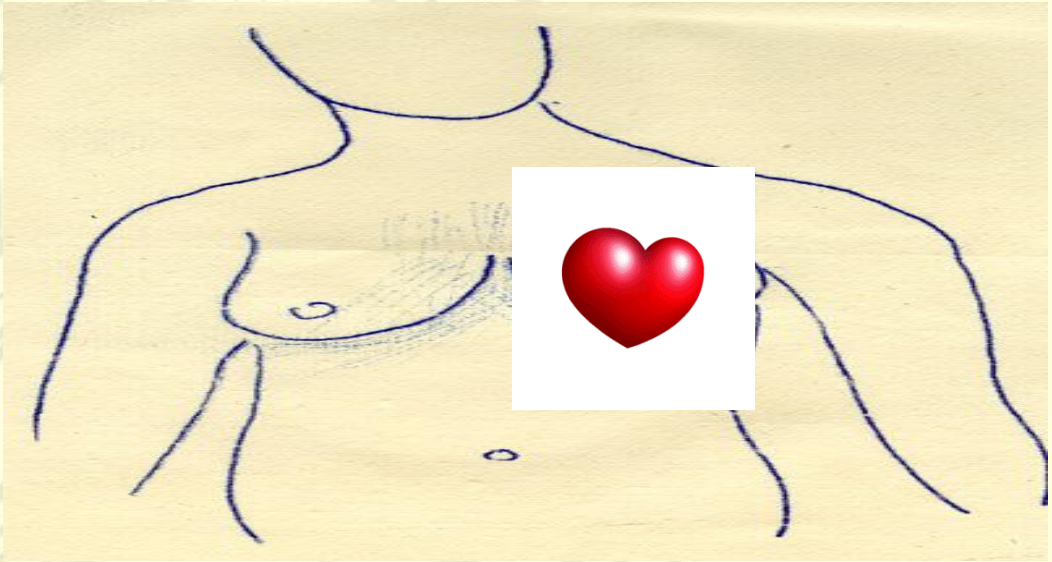
No association of laterality and HD recently



SEER: 1986-1993,no difference for any heart disease (Patt 2008)

SEER: 1992-2000, no significant association between RT and MI or the combined MI /ischemia

MI risk was higher in elderly, in pre-existing risk factors or other heart diseases

Doyle, 2007

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

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

Mortality from heart disease in 300 000 women with early breast cancer in the US SEER Cancer Registries

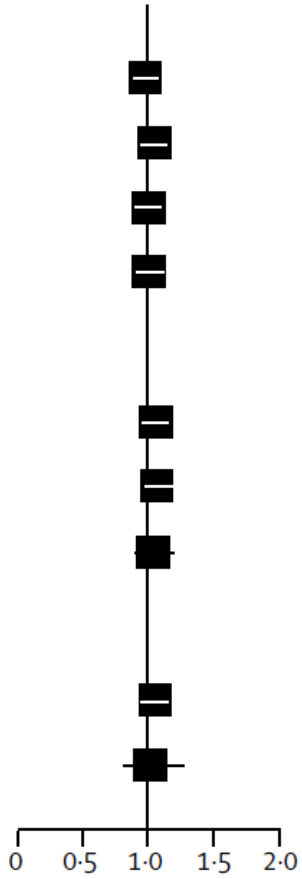
- 308 861 US women with breast cancer 1973-2001, followed until 1 Jan 2002
- 37% irradiated
- Analyses stratified for age, year of diagnosis, time since diagnosis and race

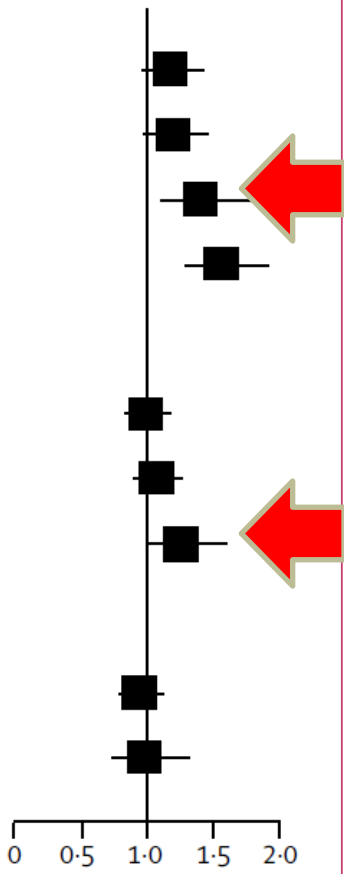
Darby et el. Lancet Oncol 2005; 6: 557-65

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

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

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





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Tasso di mortalità cardiaca (sinistra/destra)

1973-82: ***1.20 < 10 yrs***

1.42 10-14 yrs

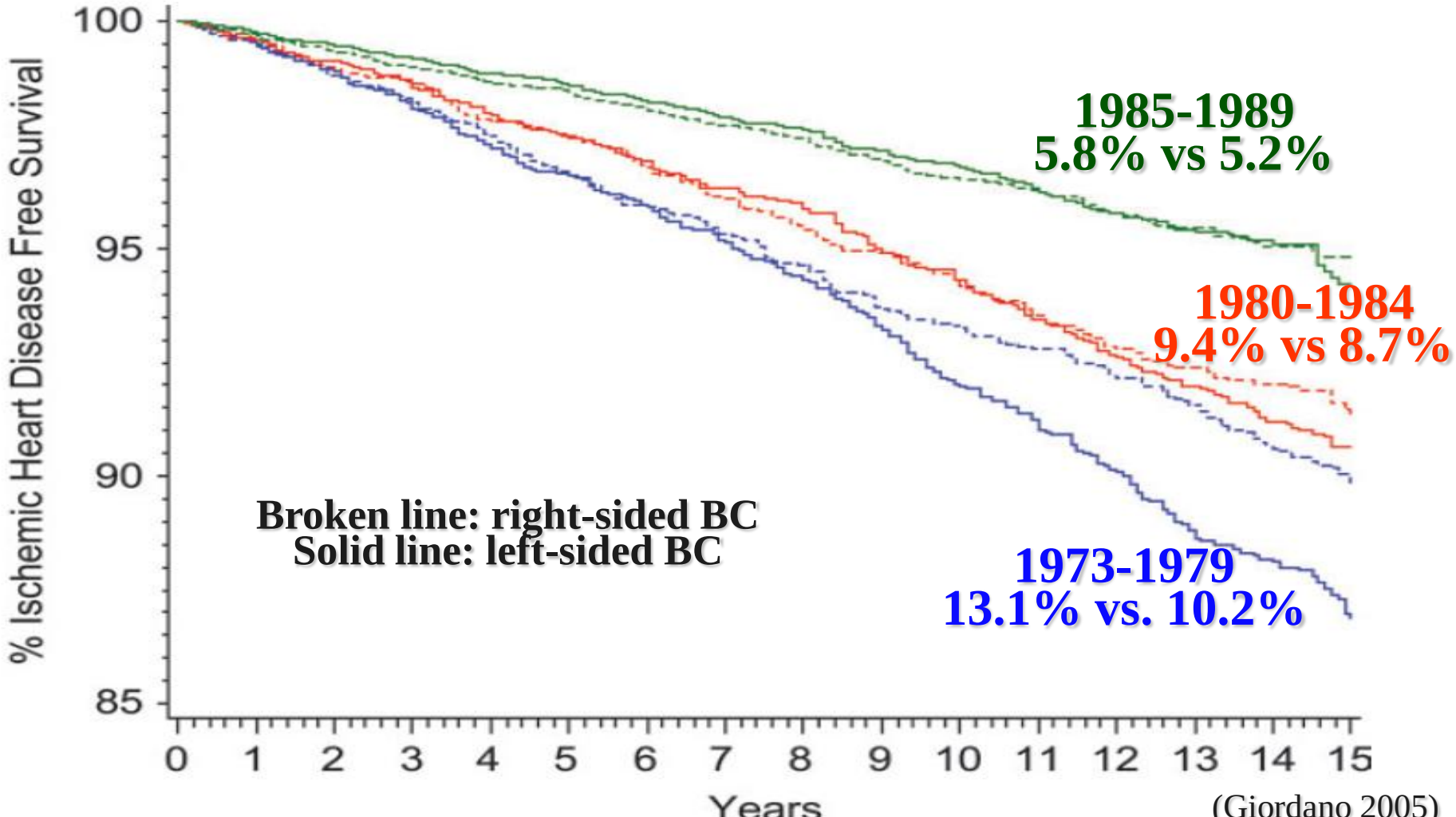
1.58 15 yrs and more

1983-92 ***1.04 < 10 yrs***

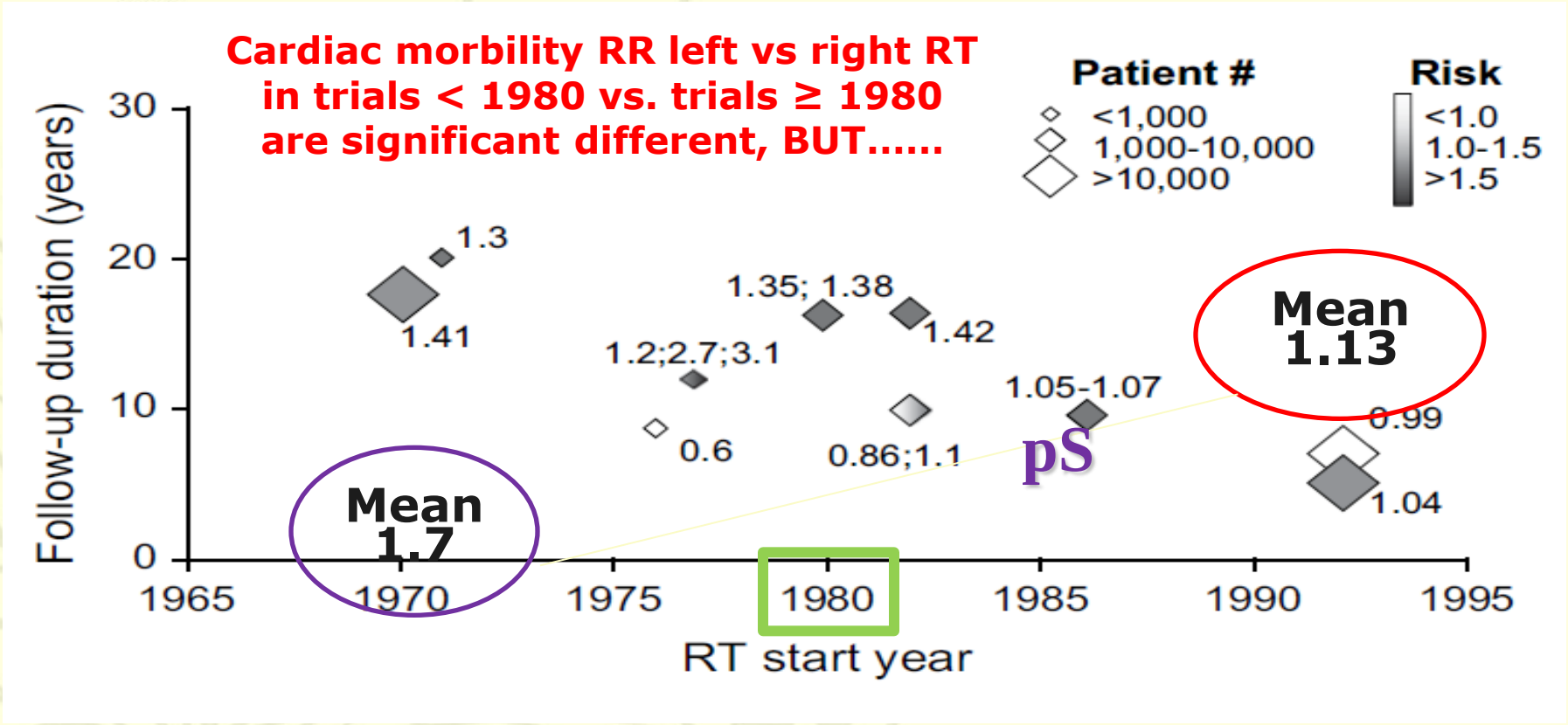
1.27 10 yrs and more

1993-2001 ***0.98 < 10 yrs***

Ischemic heart disease left vs. right RT: for each successive year 1979-1988 the HR decreased by 6%



(Giordano 2005)



All trials with a <u>median FU > 10 years</u> reported excess cardiac morbility risk, regardless of the trial start year

All modern trials, ususally with a <u>shorter FU (< 10 years)</u>, did not report excess toxicity risk: need more FU

(Demirci 2009)

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Conflicting and counfounding studies

Dose-volume

Orthovoltage energy

RT field

Patient age

Smoking

Comorbidities
Diabetes,
Hypertension

Fraction size

Length of Follow-up

Different techniques

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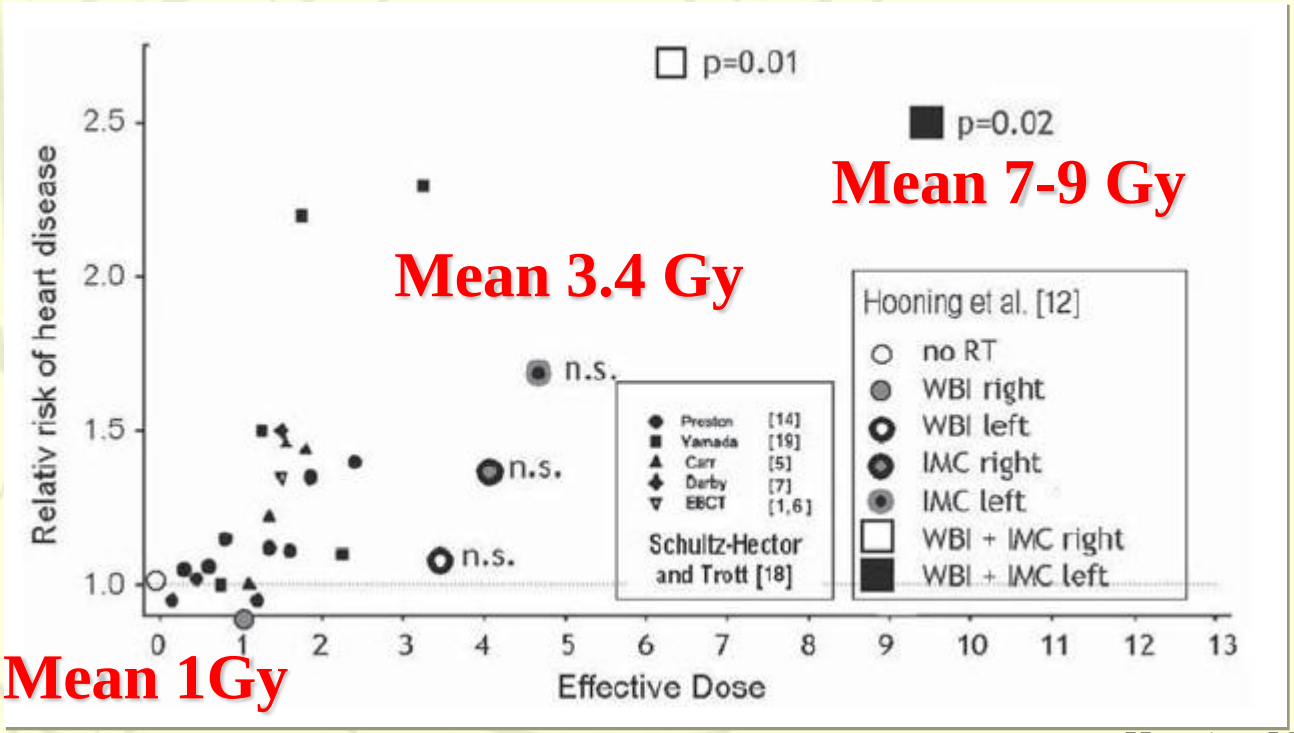
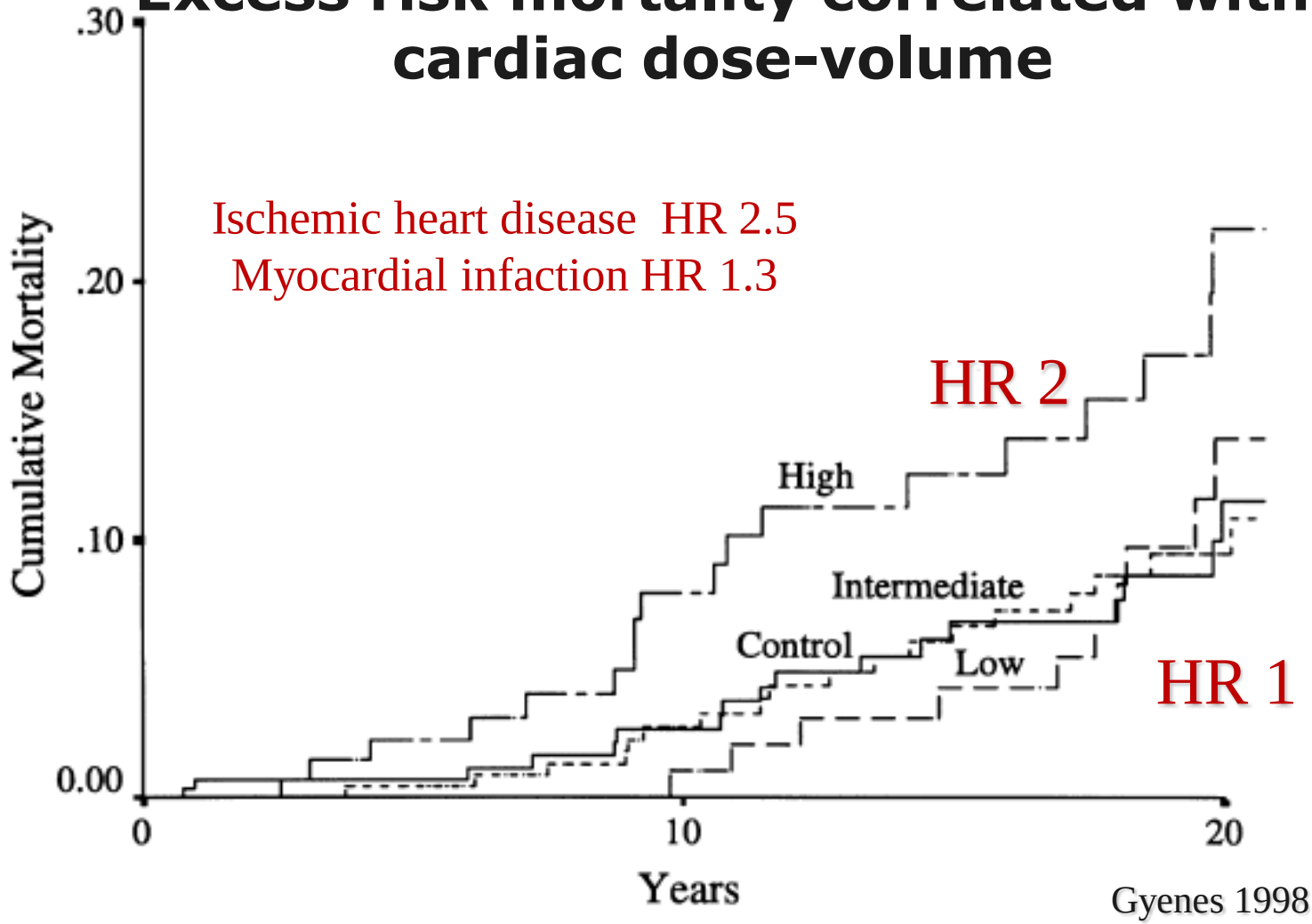
The risk of radiation -induced heart disease starts to increase at a mean heart dose of 4 Gy



Hooning J Natl Cancer Inst 2007

Excess risk mortality correlated with cardiac dose-volume

Ischemic heart disease HR 2.5
Myocardial infaction HR 1.3

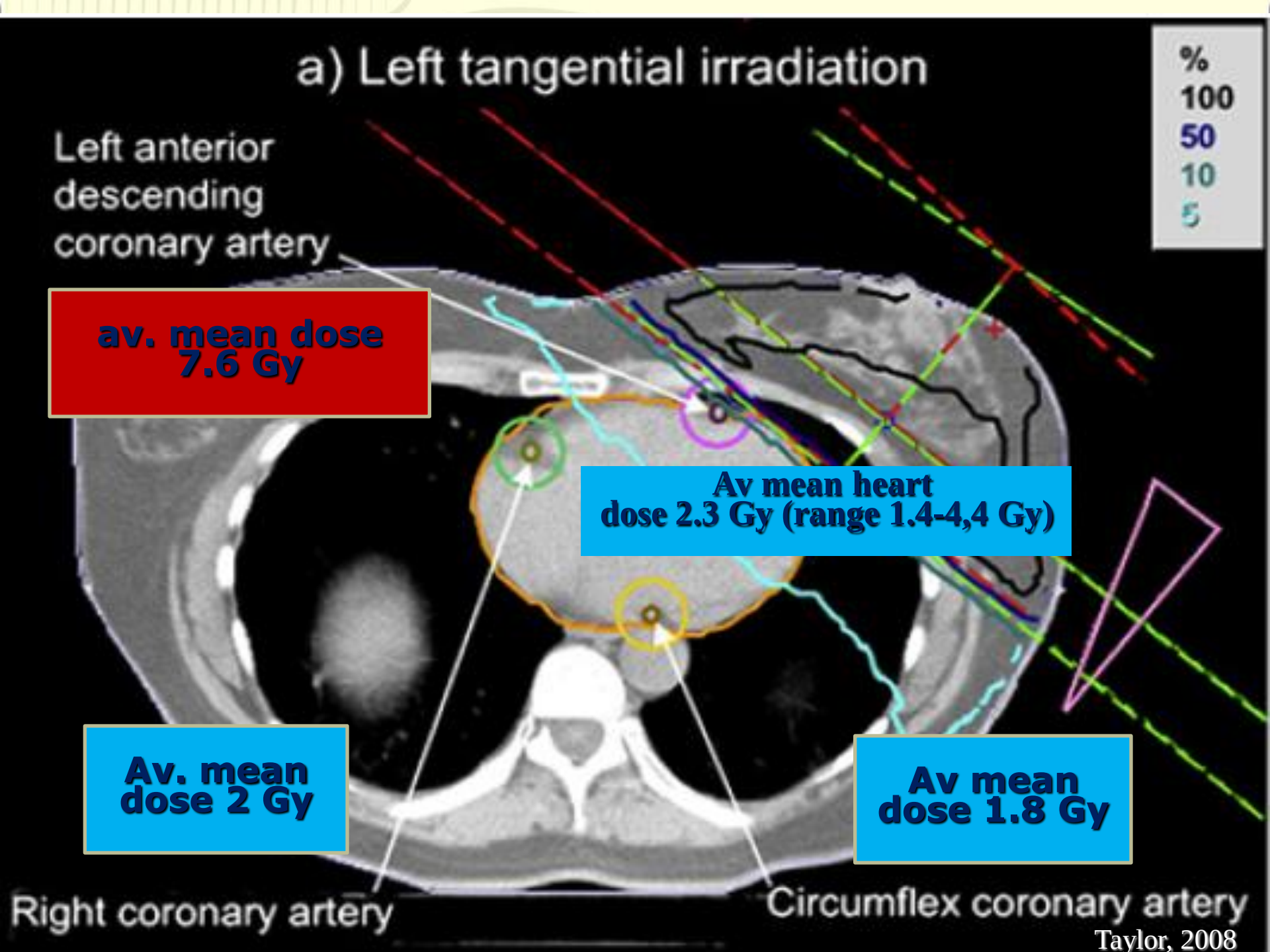


Gyenes 1998

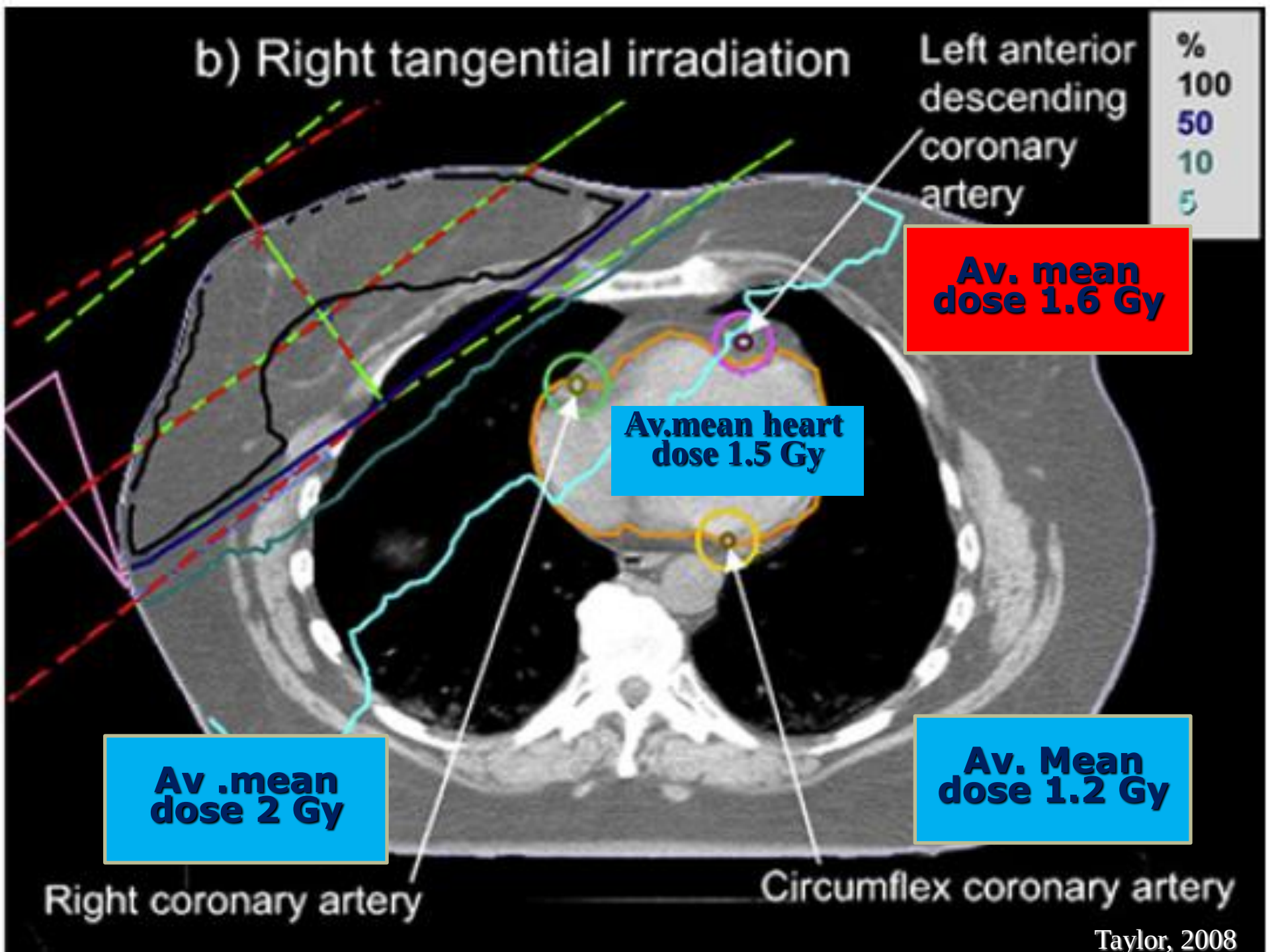
Reduction in dose to cardiac structures from left tangential radiotherapy

	Mean dose (Gy)			
Year	Heart	Left anterior descending artery	Right coronary artery	Circumflex coronary artery
1970s	13.3	31.8	9.1	6.9
1980s	4.7	21.9	2.0	2.8
2006 UK	2.3	7.6	2.0	1.2

Information supplied by C.Taylor


a) Left tangential irradiation
%
100
50
10
5
Left anterior descending coronary artery
av. mean dose 7.6 Gy
Av mean heart dose 2.3 Gy (range 1.4-4,4 Gy)
Av. mean dose 2 Gy
Av mean dose 1.8 Gy
Right coronary artery
Circumflex coronary artery

Taylor, 2008


b) Right tangential irradiation
Left anterior descending coronary artery
%
100
50
10
5
Av. mean dose 1.6 Gy
Av.mean heart dose 1.5 Gy
Av .mean dose 2 Gy
Av. Mean dose 1.2 Gy
Right coronary artery
Circumflex coronary artery
Taylor, 2008

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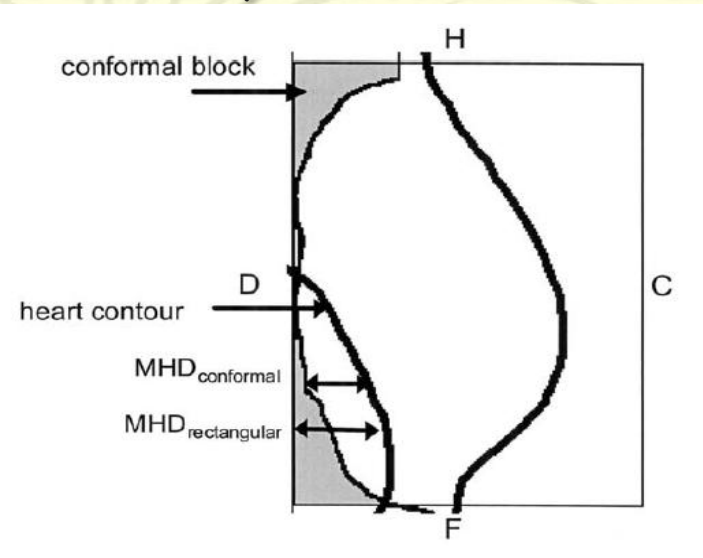
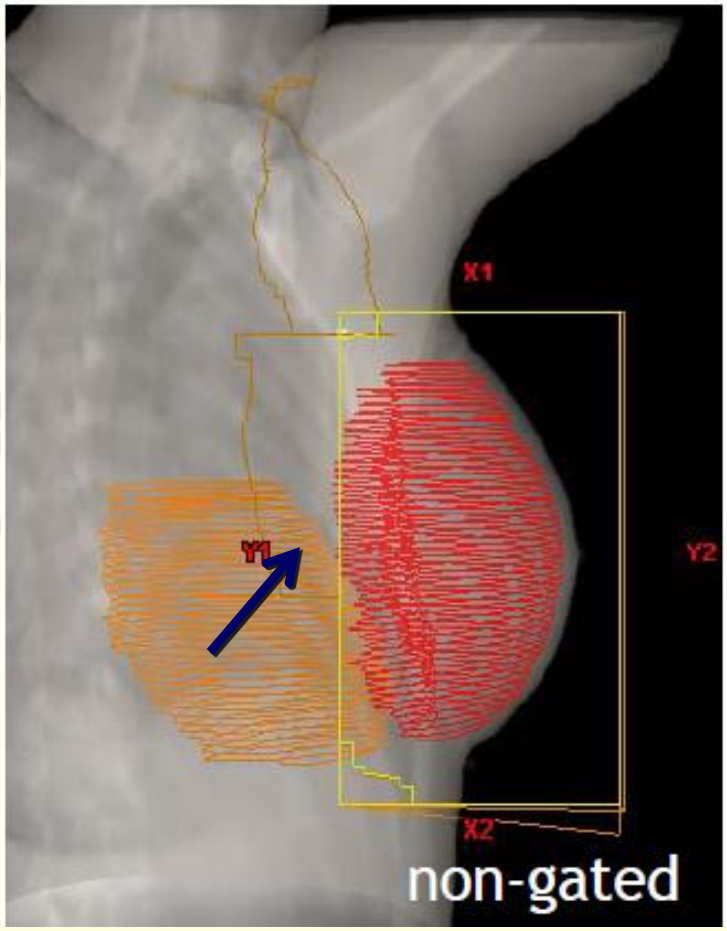
MAXIMUM HEART DISTANCE (MHD)

- Maximum distance of the heart contour to the medial field border

(on the simulator film or BEV of the medio-lateral field)

- Cardiac mortality <1% for MHD <1 cm
- Cardiac mortality >2% for MHD >2 cm





Hurkmans et al, 2000

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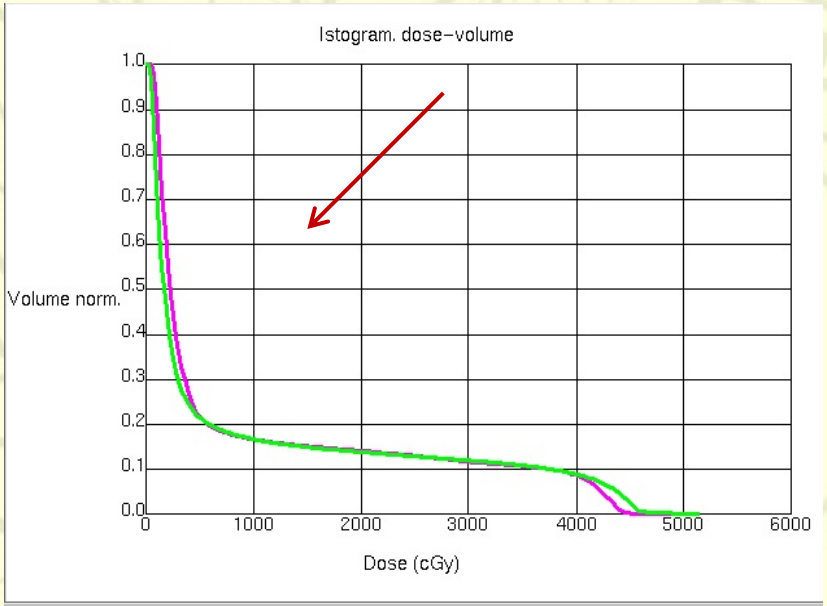
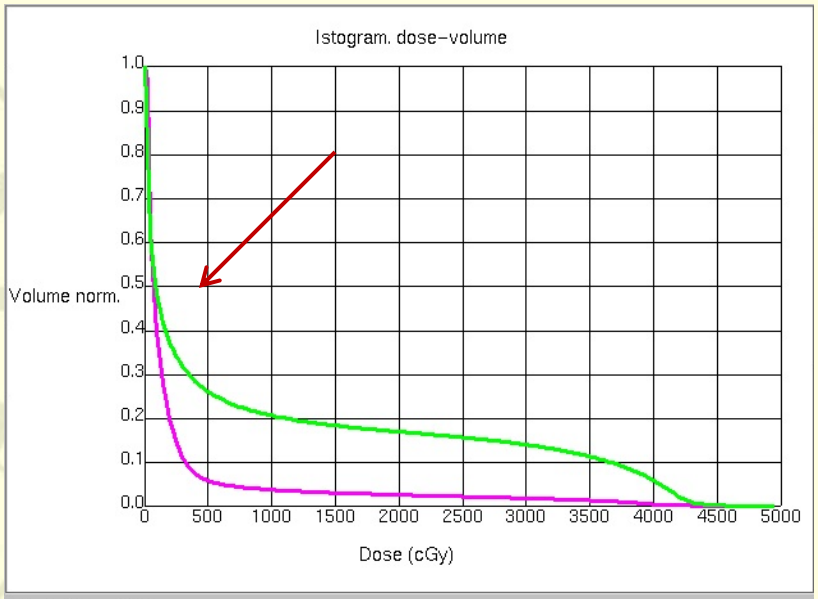
3D TREATMENT PLANNING

DOSE VOLUME HISTOGRAMS



Statistiche ROI

Tipo linea	ROI	Prova	Min.	Max.	Media	Dev. std.
	cuore	Trial_2	53.9	4504.4	767.4	1272.4
	polm sin	Trial_2	29.1	4881.9	737.6	1321.0



Statistiche ROI

Tipo linea	ROI	Prova	Min.	Max.	Media	Dev. std.
	cuore	Trial_IMRT	17.0	4297.3	209.6	533.3
	polm sin	Trial_IMRT	9.7	4560.4	769.2	1337.1

Heart: left breast

- **15% of the heart < 25 Gy**
- **5% of the heart < 5 Gy**

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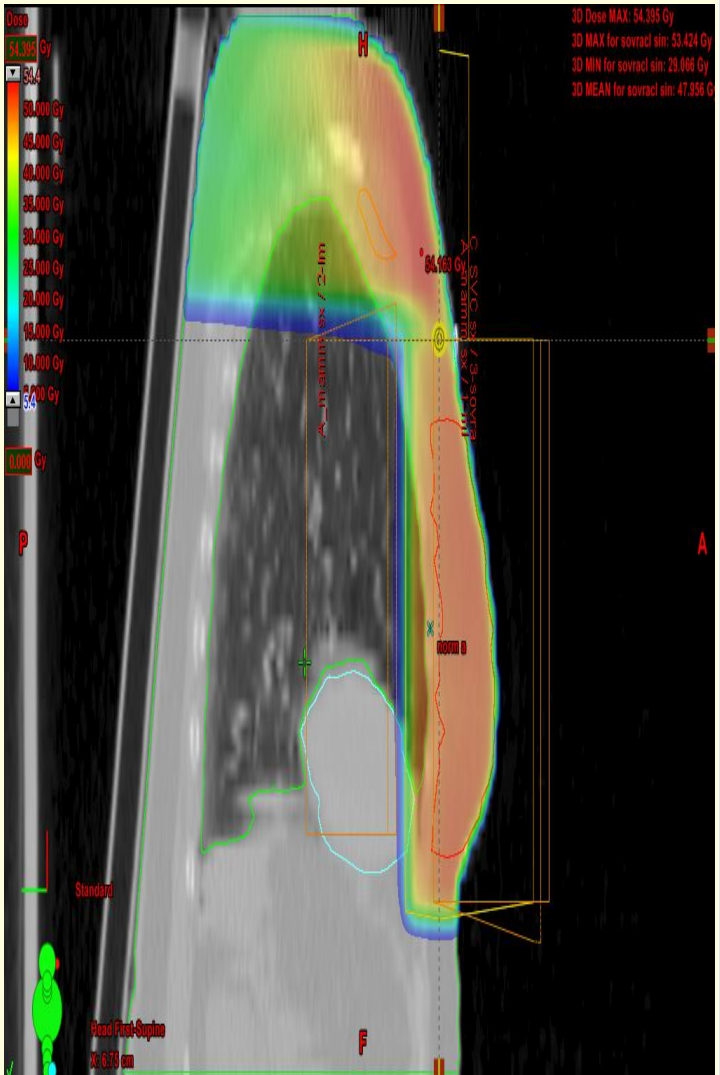
Volume cardiaco irradiato: Mammella

Significativa associazione con:

- ***Quale target: es +/- N locoregionali***
- ***Tecnica di trattamento***



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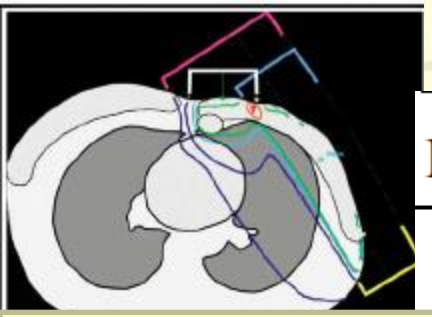
THE CONTRIBUTION OF REGIONAL IRRADIATION AND BOOST DOSE

- **Left or right sided scar (boost): mean dose < 0.3 Gy**
- **Left-sided axillary RT: mean dose 0.4 Gy**
- **Left supraclavicular field: mean dose 0.6 Gy**
- **IMN RT: mean dose ranging 2 Gy-13 Gy**

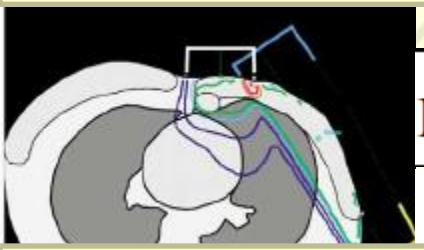
(Taylor 2008)

Mean dose (Gy) and % volume of heart



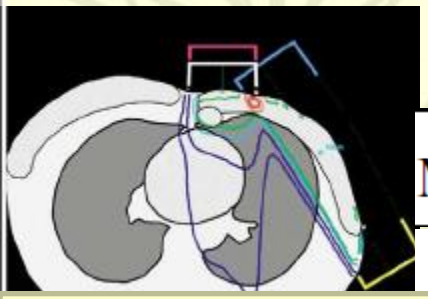
Mean dose	V30
8.7 (3.5)	7.4 (5.8)

Paramixed technique



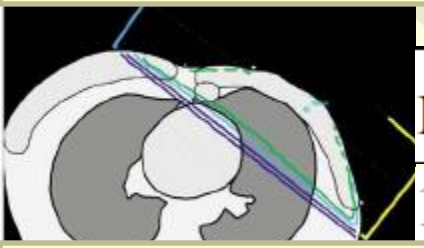
Mean dose	V30
7.5 (2.6)*	7.1 (5.3)

Patched technique



Mean dose	V30
12.9 (3.8)*	9.6 (5.7)

Standard technique



Mean dose	V30
11.1 (4.4)*	16.0 (9.2)

Partial wide tangents

EORTC year 3 (2004)	No IM-MS N (%)	IM-MS N (%)	P-value
Cardiac fibrosis	5 (0.3%)	7 (0.4%)	0.5
Evidence of cardiac disease	28 (1.4)	31 (1.6)	0.6

EORTC: 26 Gy X+ 24 Gy e-

Van Der Laan , 2005

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Recommended dose/volume limits (Gagliardi, 2010)

essentially eliminate the heart from the primary beams. If NTCP models for cardiac mortality are used, it should be considered that an NTCP value ≥5% could jeopardise the beneficial effect on survival of RT (1). So as not to underestimate this risk, the most conservative approach is provided by the use of the steeper dose–response curve (Fig. 1), that is, the one from the breast data (25). For partial irradiation, conservative (NTCP) model-based estimates predict that a V_{25Gy} < 10% (in 2 Gy per fraction) will be associated with a <1% probability of cardiac mortality ~15 years after RT. For this a conservative (*i.e.*, overly safe) model was used that may overestimate the risk. Conversely, as the

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Conflicting and counfounding studies

Dose-volume

Orthovoltage energy

RT field

Patient age

Smoking

Comorbidities
Diabetes,
Hypertension

Length of Follow-up

Fraction size

Different techniques

Hypofractionated RT

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Do large fractions increase the risk?

The priority is to protect the heart as much as possible whatever dose regimen is used

Yarnold,2010

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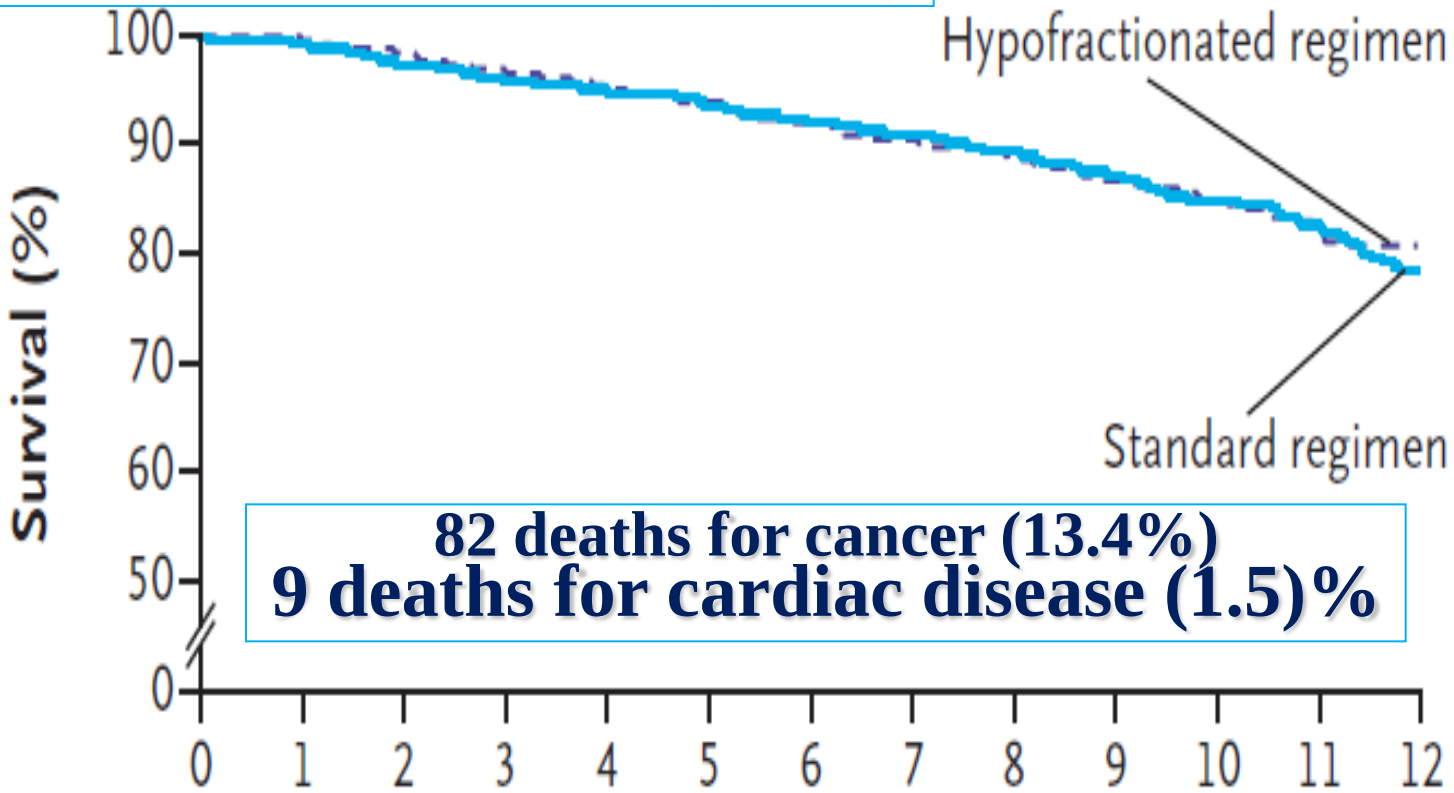
Ontario Clinical Oncology Group Trial

82 deaths for cancer (13.2%)
12 deaths for cardiac disease (1.9%)



82 deaths for cancer (13.4%)
9 deaths for cardiac disease (1.5)%

Med FU 10 years

Whelan 2010

No difference in cardiac mortality with hypofractionated (40 Gy/16 or 42.5 Gy/16) vs conventional RT irrespective of laterality

>7000 pts , 1984-2000

Age (y)	Fraction size (Gy)	Laterality	Cumulative incidence of cardiac death at 10-y follow-up (%)	Relative risk* at 10-y follow-up
All ages	≤2	Right	1.01	**1.00**
		Left	0.96	0.95 (0.24–3.78)
	>2	Right	1.73	**1.00**
		Left	1.86	1.07 (0.68–1.69)
≤60	≤2	Right	0.00	**1.00**
		Left	0.00	N/A
	>2	Right	0.70	**1.00**
		Left	0.34	0.49 (0.15–1.62)
>60	≤2	Right	2.68	**1.00**
		Left	2.37	0.90 (0.23–3.53)
	>2	Right	3.05	**1.00**
		Left	3.74	1.22 (0.75–2.01)

Vallis, 2002,Marhin, 2007

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Conflicting and counfounding studies

Dose-volume

Orthovoltage energy

RT field

Patient age

Smoking

Comorbidities
Diabetes,
Hypertension

Fraction size

Length of Follow-up

Different techniques

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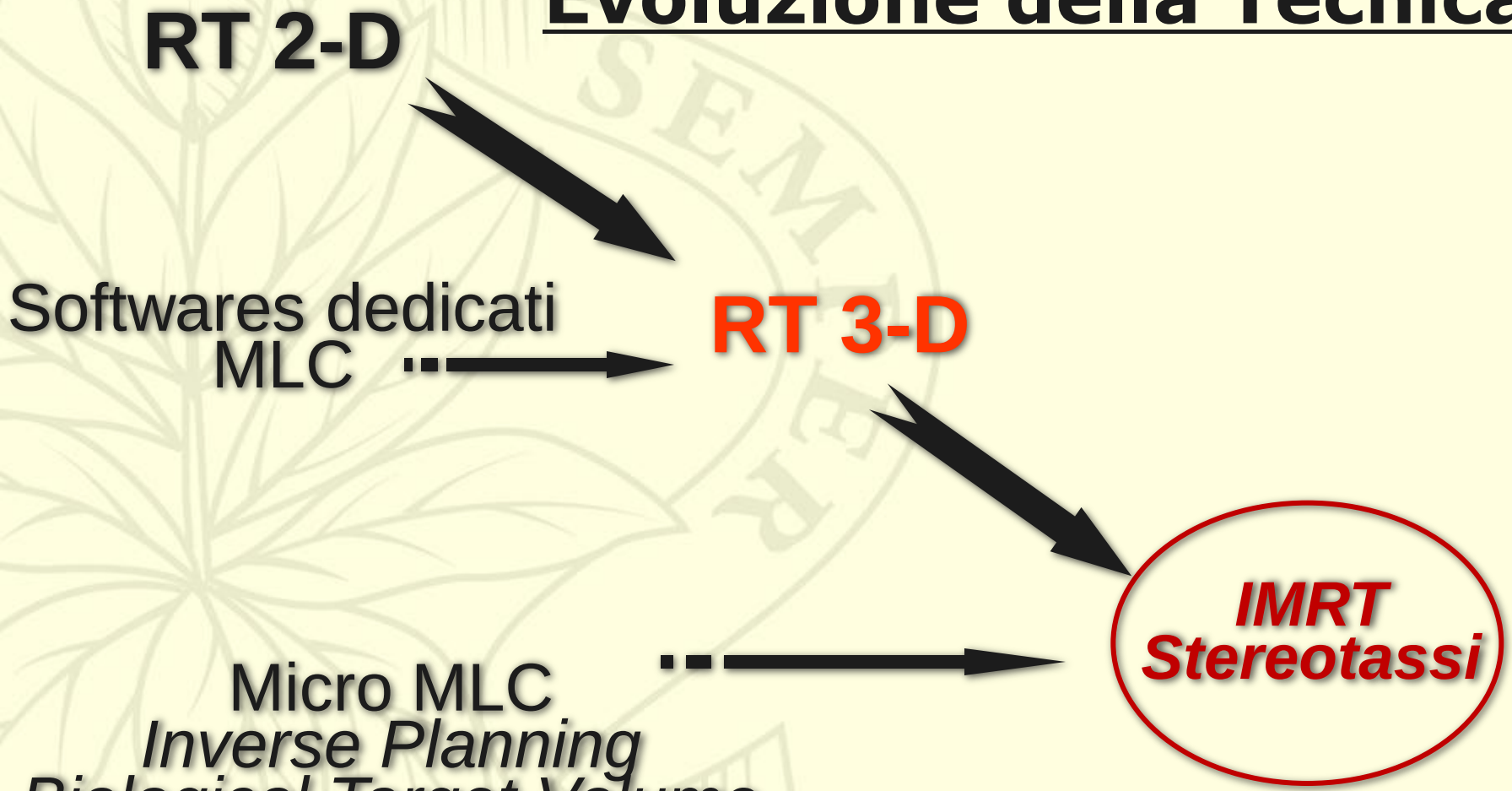
Evoluzione della Tecnica



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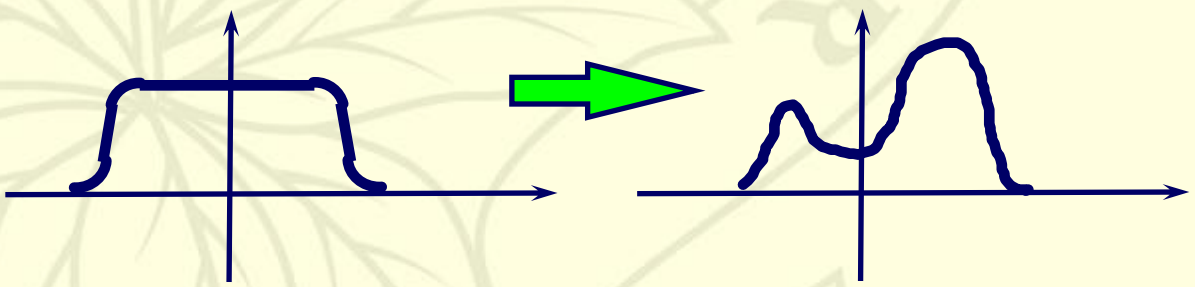
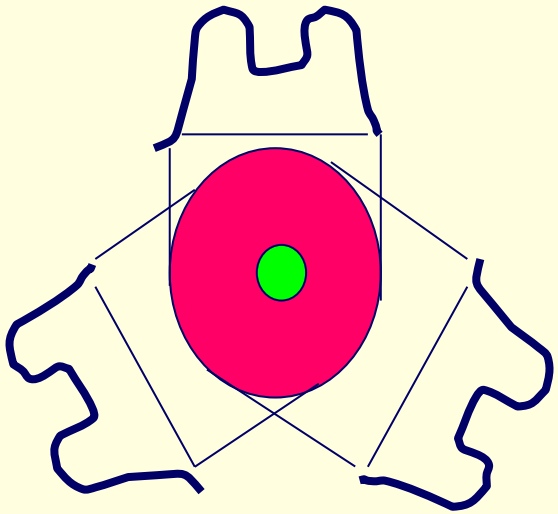
RT ad intensità modulata (IMRT)

Tecnica di RTP 3D conformazionale che ottimizza l'irradiazione di volumi irregolari

Per bersagli complessi o in prossimità di organi critici la distribuzione della dose è ottenuta mediante fasci di radiazioni con fluenza non uniforme





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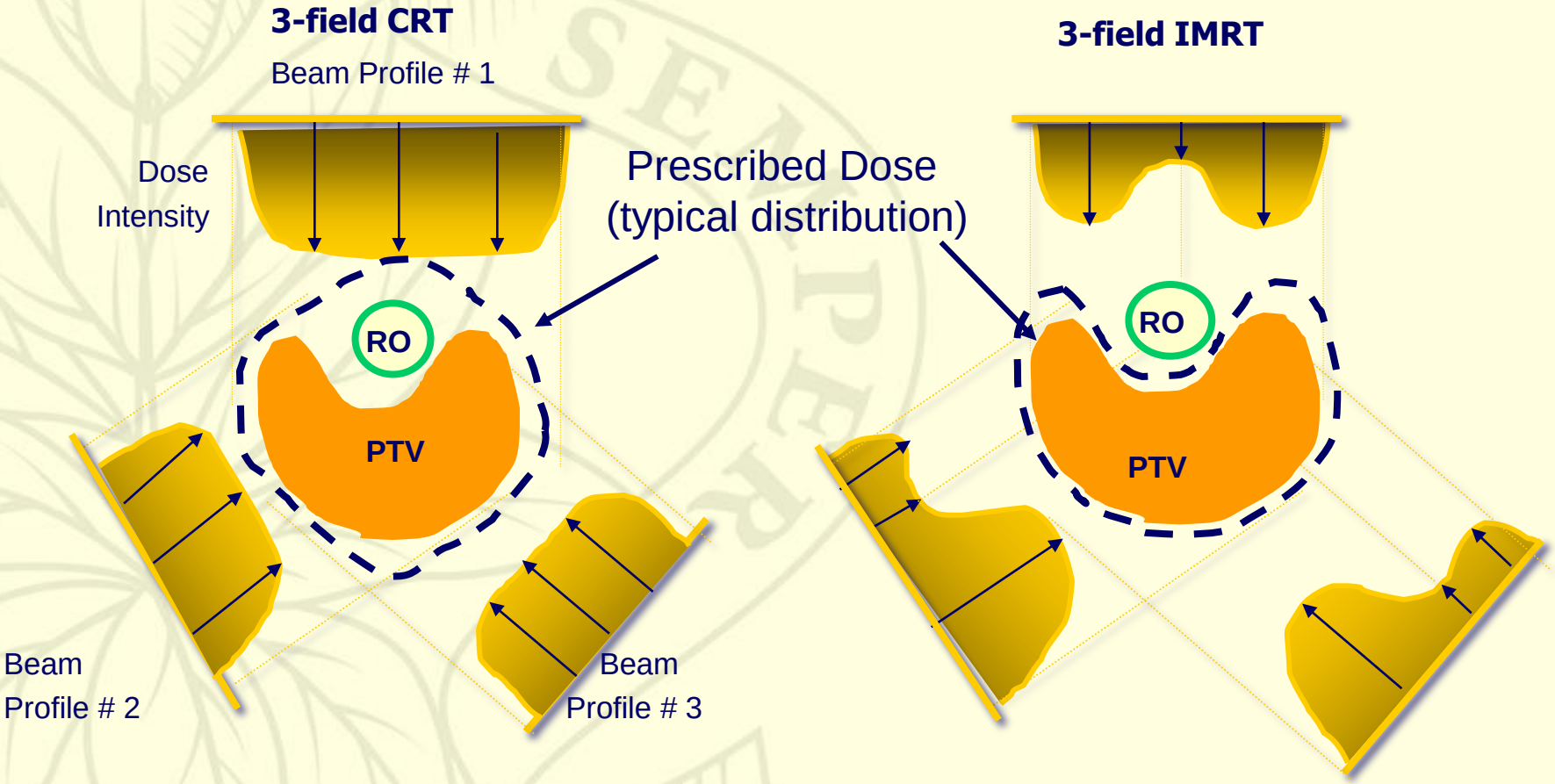
3D-CRT vs. IMRT



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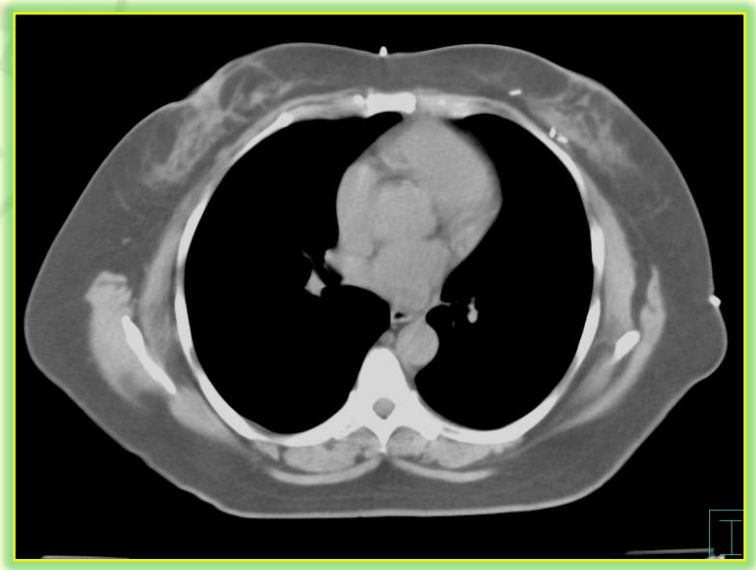
RT con tecniche di controllo del respiro

I movimenti respiratori nell'irradiazione della mammella possono avere un peso variabile tra paziente e paziente, riflettendosi in problemi di riposizionamento, piuttosto che sulla qualità del trattamento.

Il maggior vantaggio del **controllo del respiro in inspirazione** è la possibilità di dislocare il cuore verso il mediastino, allontanandolo dai campi di trattamento.



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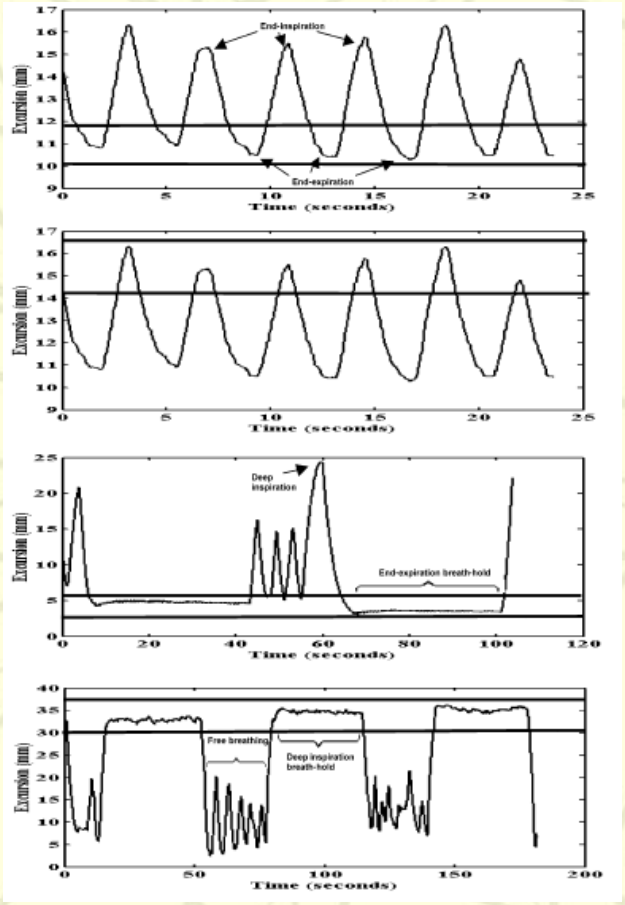
RT con tecniche di controllo del respiro



end-expiration gating

end-inspiration gating

end-expiration breath hold

deep inspiration breath hold

Korreman *Radiotherapy and Oncology 76 (2005) 311–318*

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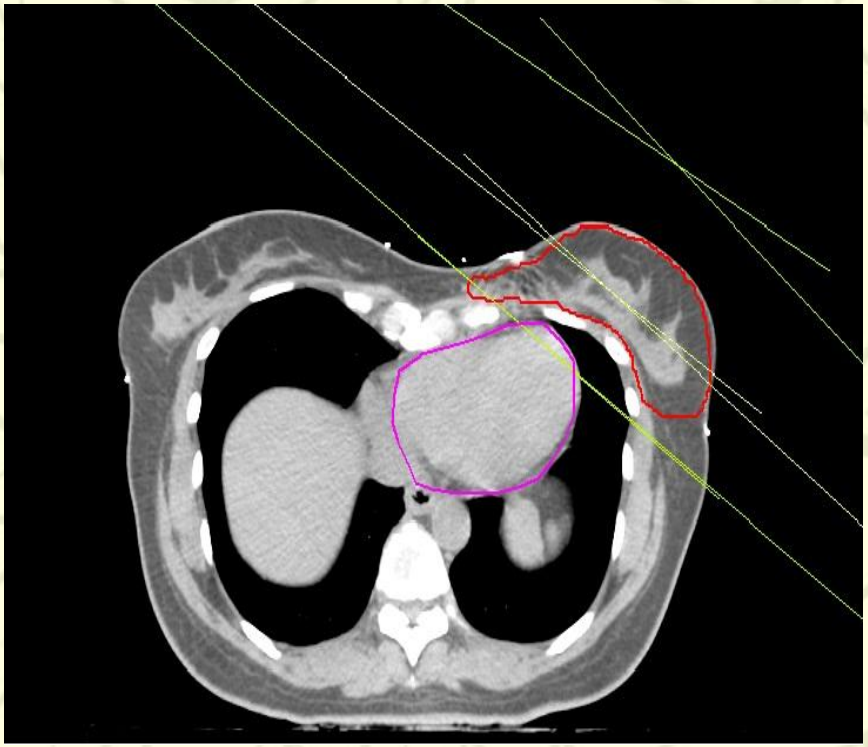
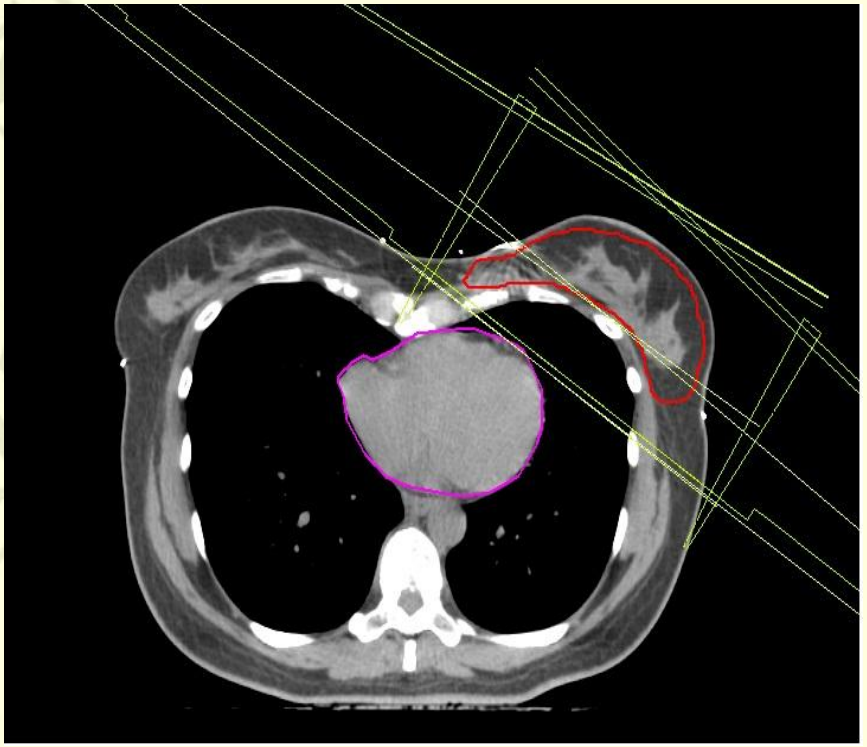
I.R.C.C.S.

RT con tecniche di controllo del respiro



Free Breathing



Deep Inspiration Breath Hold

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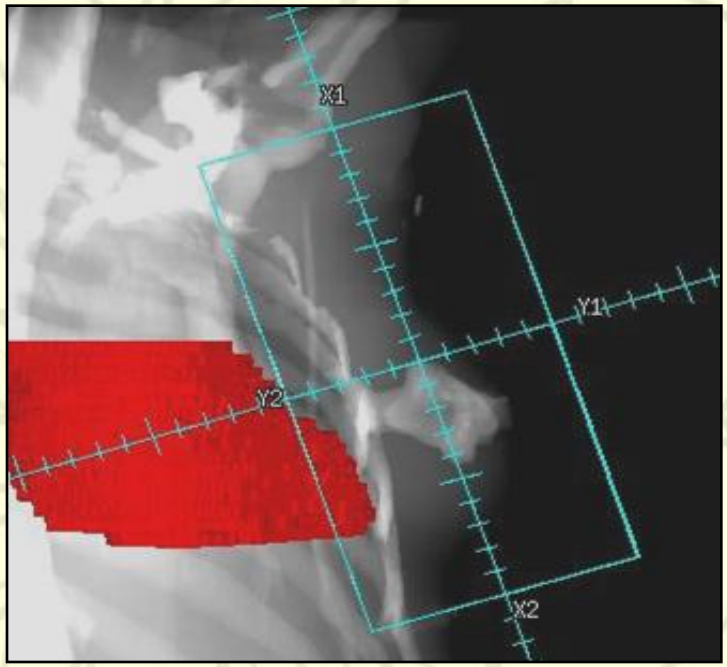
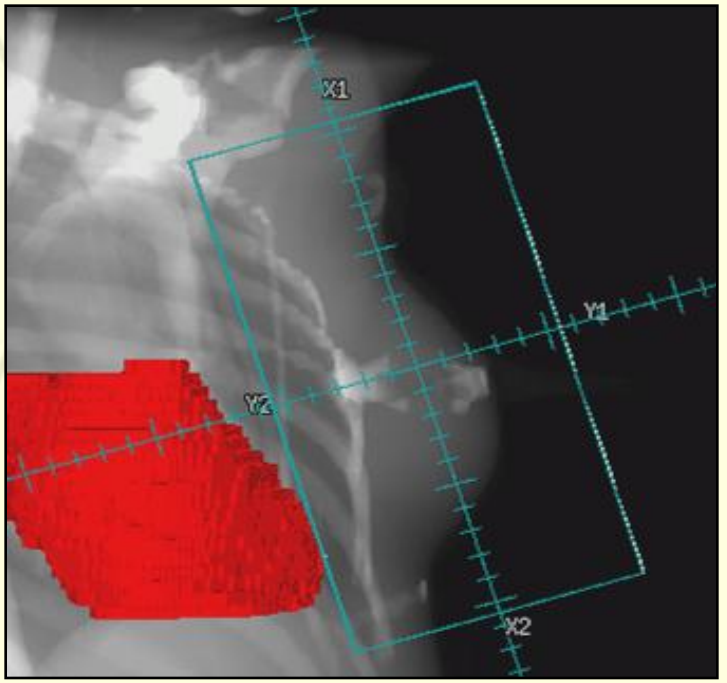
RT con tecniche di controllo del respiro



Free Breathing



Deep Inspiration Breath Hold

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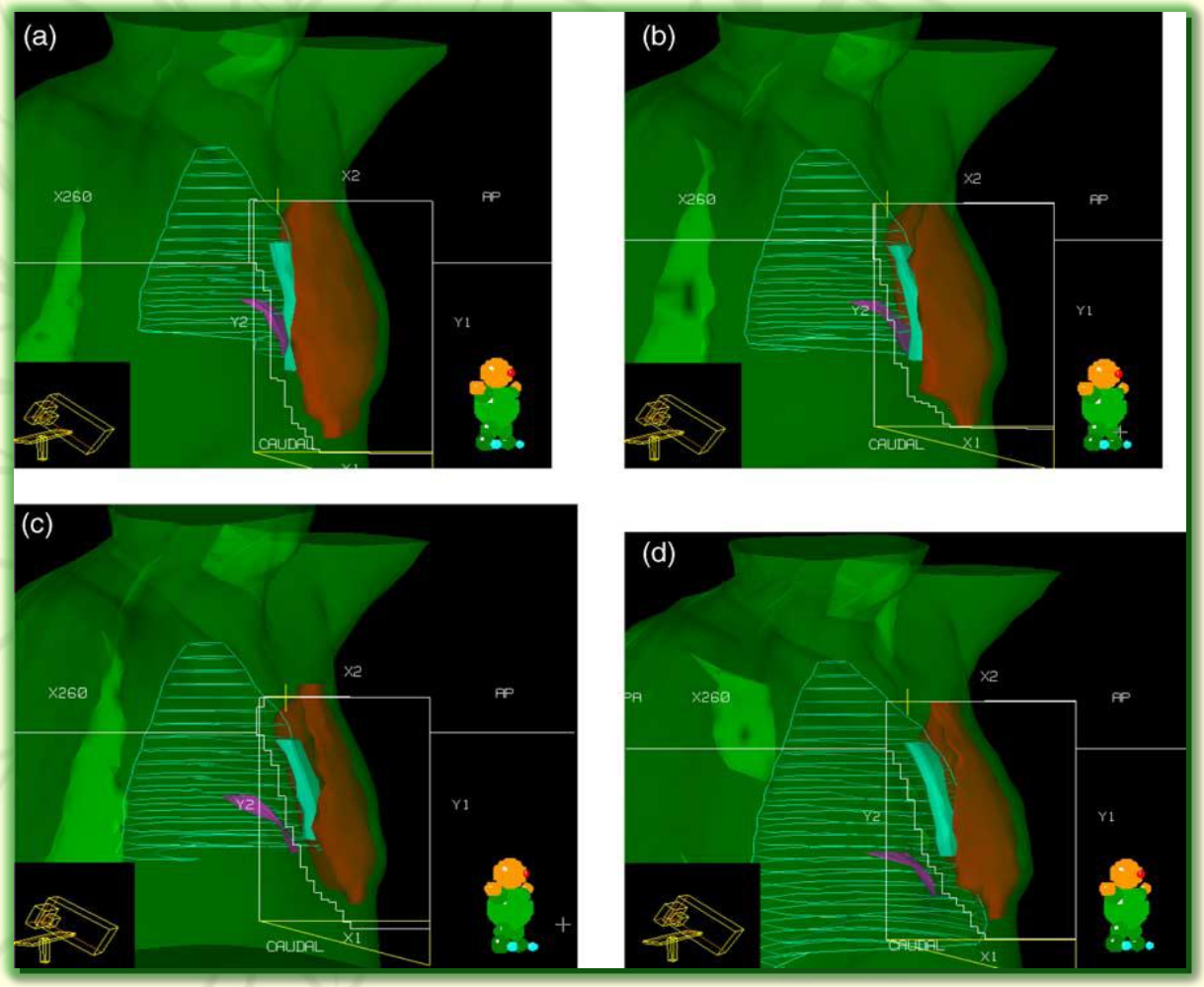
RT con tecniche di controllo del respiro



a) end-expiration breath hold

b) end-inspiration gating

c) end-expiration gating

d) deep inspiration breath hold

Korreman *Radiotherapy and Oncology 76 (2005) 311–318*

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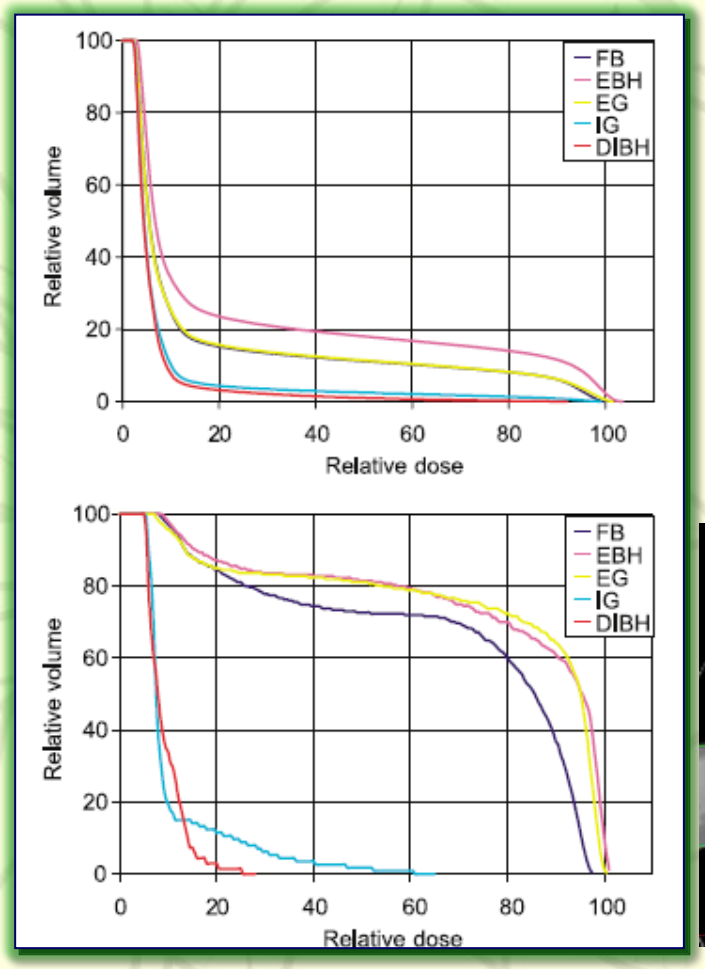
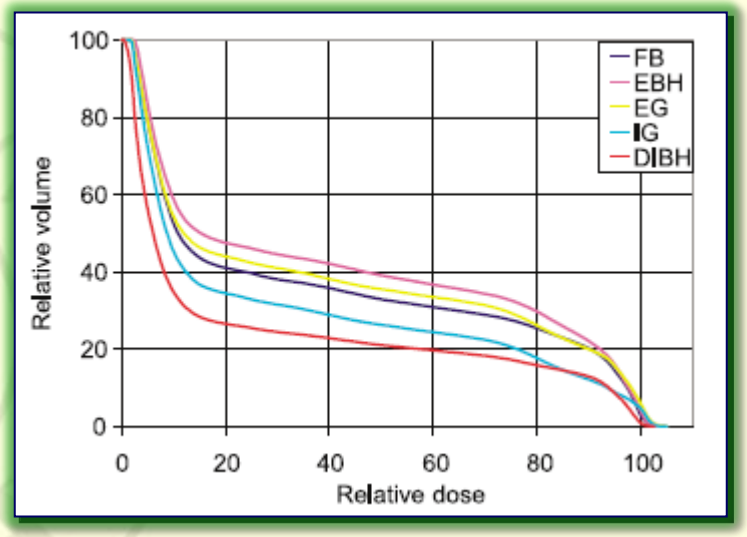
RT con tecniche di controllo del respiro

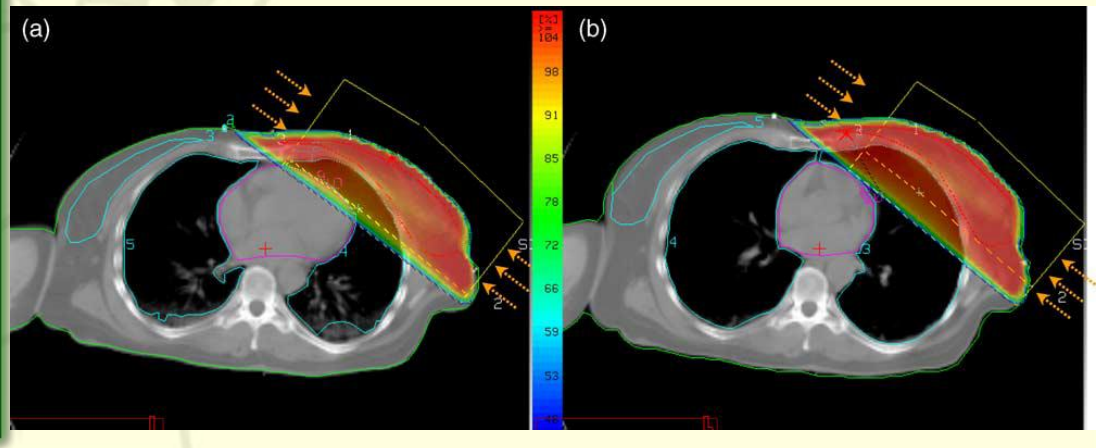
CUORE



LADCA

POLMONE





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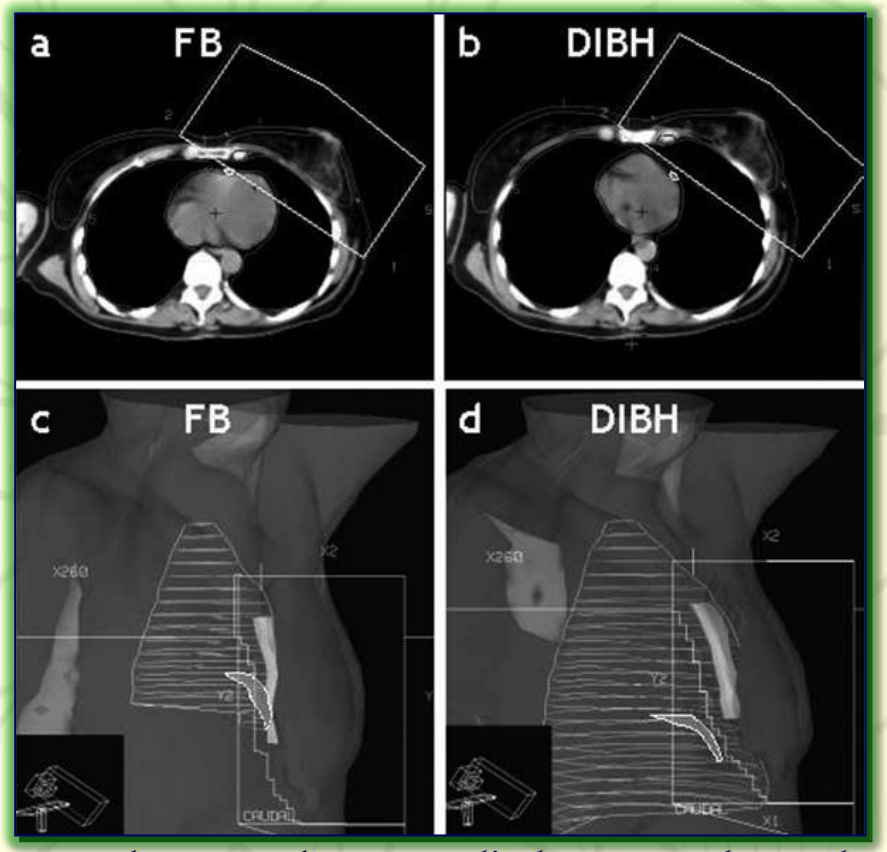
RT con tecniche di controllo del respiro



Volume relativo mediano che riceve >50% della dose prescritta

	FB	DIBH
Polmone	37%	31%
Cuore	8%	1%
LADCA	54%	5%

Anders N. Pedersen *Radiotherapy and Oncology 72 (2004) 53–60*

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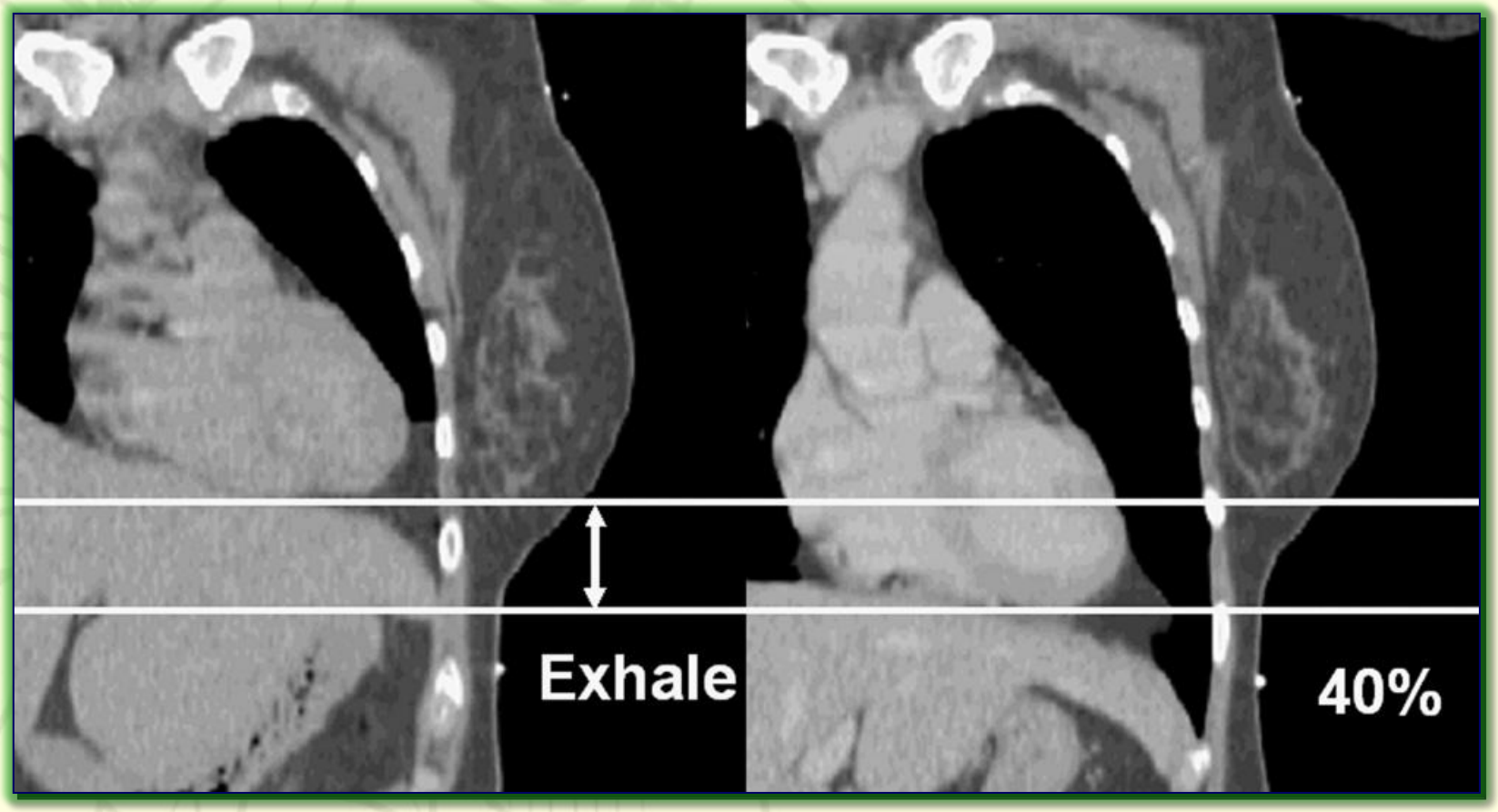
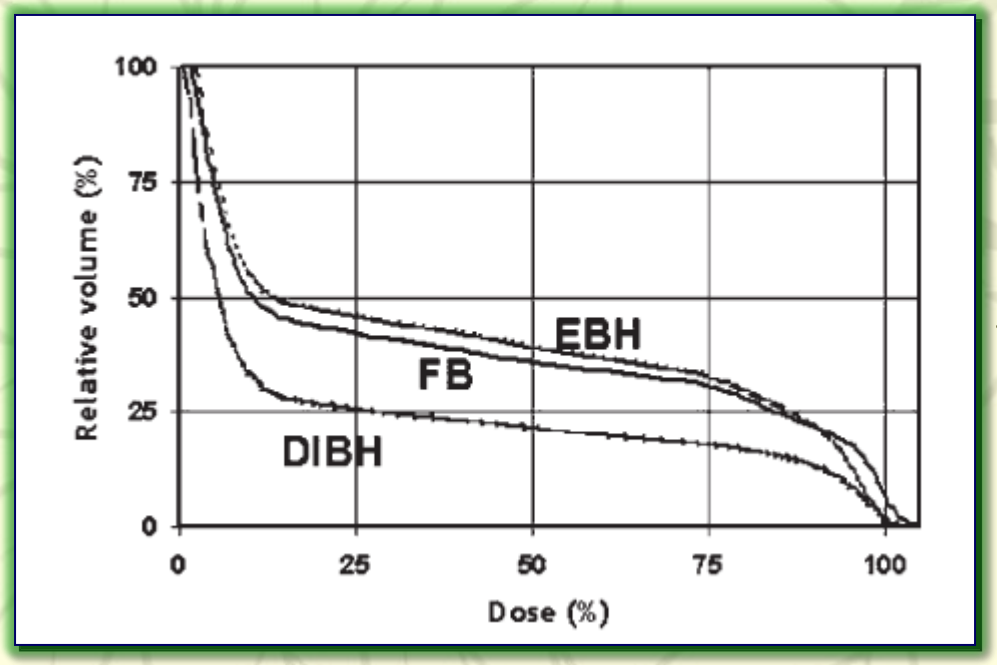
RT con tecniche di controllo del respiro



RT con tecniche di controllo del respiro



Confronto tra DVH del polmone omolaterale in EBH, FB, DIBH

Anders N. Pedersen *Radiotherapy and Oncology 72 (2004) 53–60*

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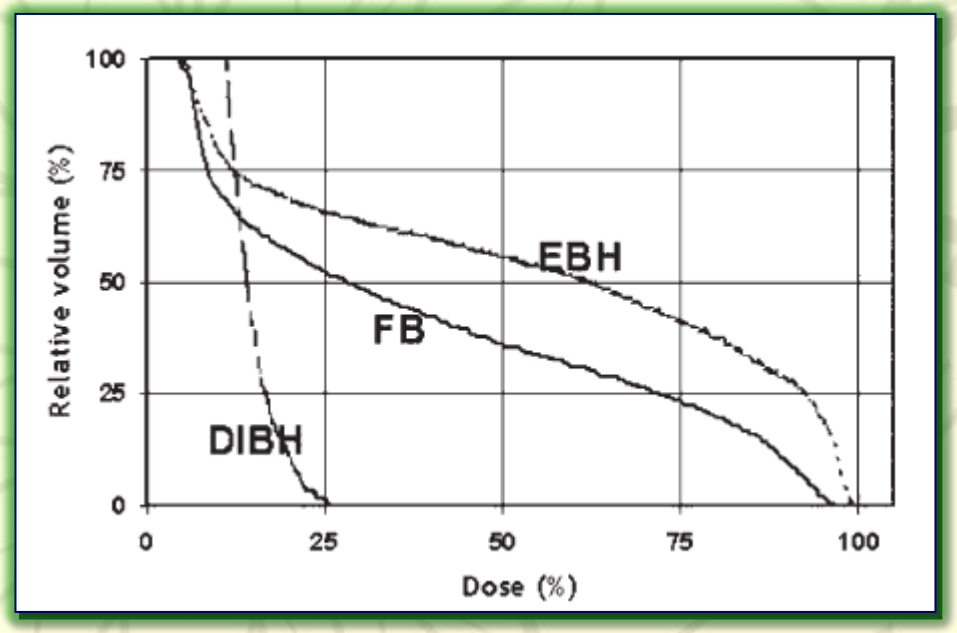
RT con tecniche di controllo del respiro



Anders N. Pedersen *Radiotherapy and Oncology 72 (2*

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RT con tecniche di controllo del respiro

Volume relativo e assoluto di cuore e LADCA che riceve >50% della dose prescritte

Patient no.	Free breathing	
	Heart	LADCA
1	3% (18.5)	36% (1.7)
2	12% (82.7)	45% (2.6)
3	20% (130.7)	79% (2.5)
4	1% (4.2)	12% (0.4)
5	8% (42.9)	68% (2.4)
6	4% (19.7)	74% (1.8)
7	7% (48.9)	58% (2.0)
Median	8%	54%

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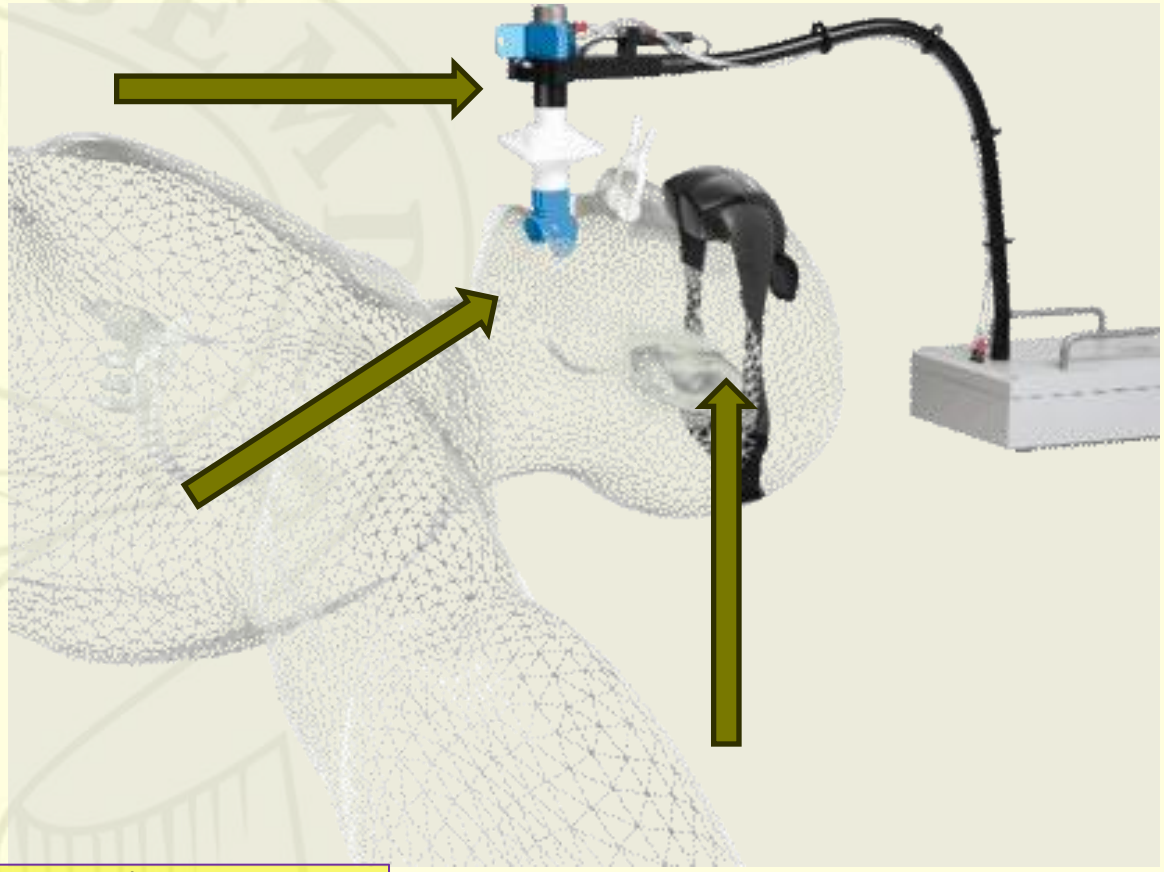
RT con tecniche di controllo del respiro

- Il respiro viene misurato tramite uno spirometro collegato alla bocca per mezzo di un boccaglio;
- un tappanaso impedisce una respirazione nasale.

- Il paziente segue l'andamento del proprio respiro tramite un paio di «video-occhiali»



Sistema spirometrico

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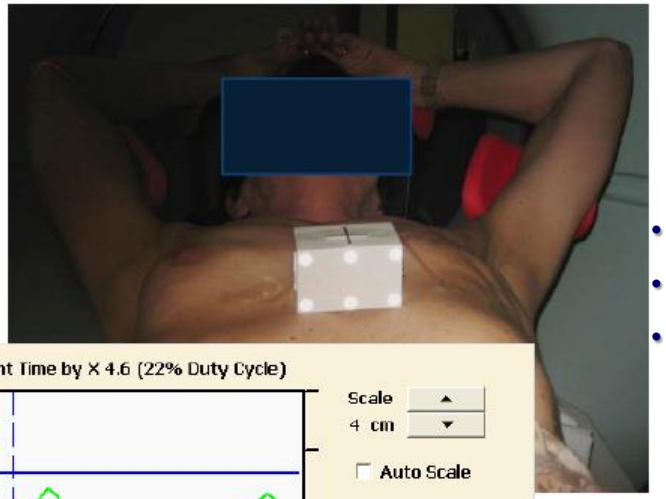
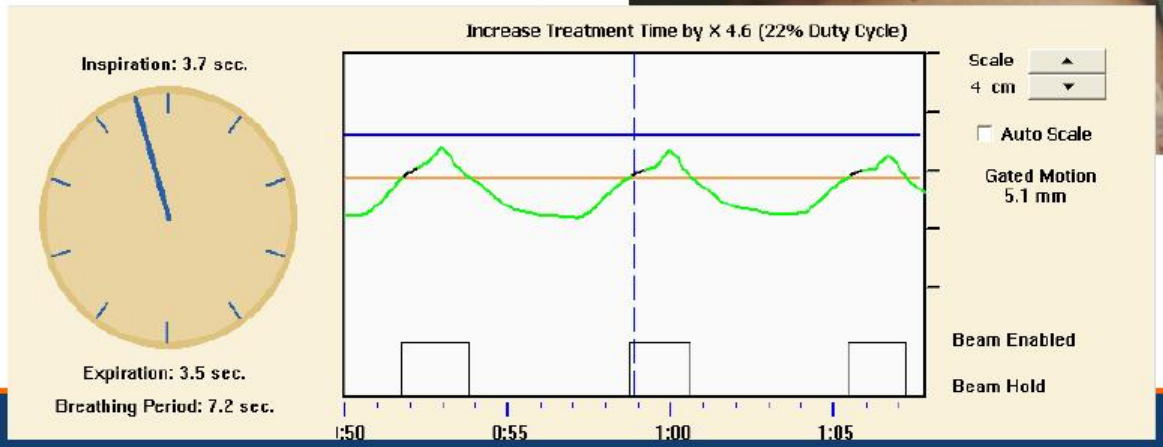
RT con tecniche di controllo del respiro

- Gating using Real time Positioning Managment
  - External
  - Not invasive
  - High patient compliance
  - Easy



- Telecamera fissa ad infrarossi
- Marker block riflettenti sulla pz
- Software dedicato interfacciato col CLINAC



VARIAN medical systems

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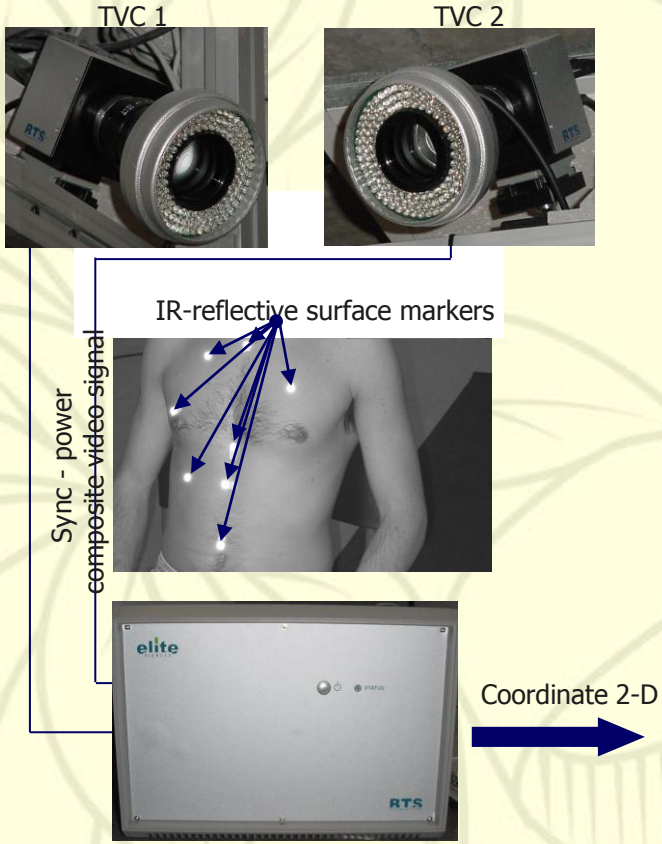
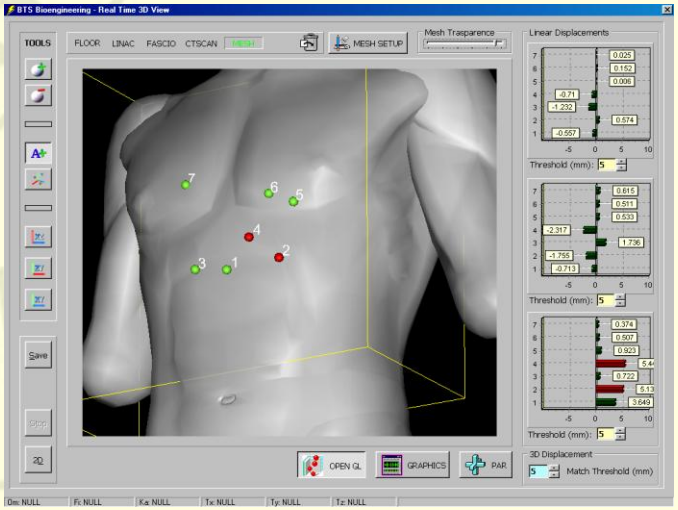
Irradiazione con tecniche di controllo del respiro

Localizzazione opto-elettronica a marker passivi



- **Telecamere con flash all'infrarosso**
- **Marcatori riflettenti**
- **Software per *image-processing* e ricostruzione tridimensionale**



CT SCAN ACQUISITION

1. 6 reflective markers placed on selected skin landmarks

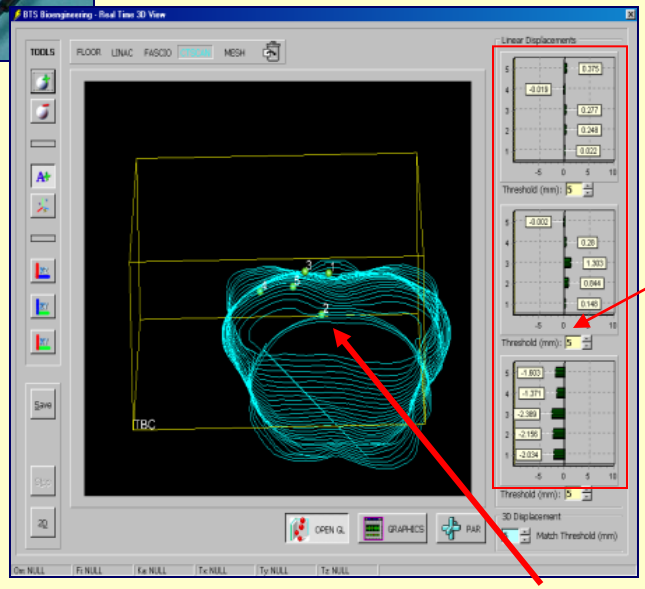
2. acquisition of 3D marker positions at a comfortable level of DIBH, as reference

3. eyewear viewer (MicroOptical Co. USA) connected to the ELITE computer, showing the real time marker displacements in all directions

4. evaluation of breath hold duration

5. CT - scan (3 mm slices) at free breathing (FB) for treatment planning comparison

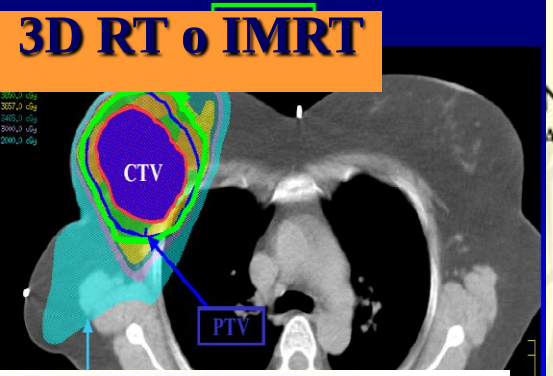
6. CT scan (3 mm slices) at breath hold (BH) in 3 slot (~ 25 slices), with real time monitoring of markers displacement in all directions



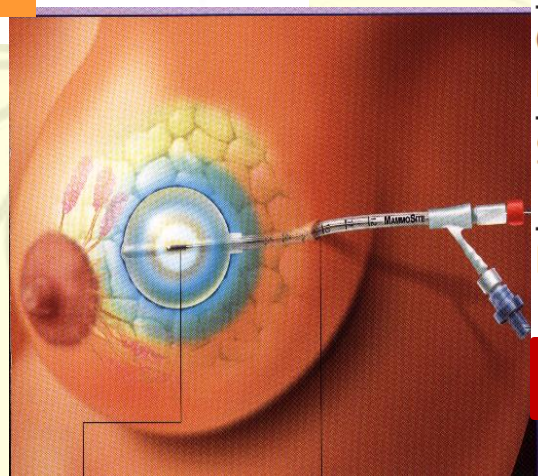
MARKER DISPLACEMENTS CALCULATION

MARKERS 3D LOCALIZATION

3D RT o IMRT



Targit



IORT

Brachiterapia HDR/LDR

Partial breast irradiation

Technique	PBSI	HDR (catheters)	Wedge	IMRT	3D-CRT
Treated Breast	90 Gy	34 Gy	50 Gy	50 Gy	38.5 Gy
Contralateral Breast	2.2 mSv	230 mSv	1695 mSv	206 mSv	140 mSv
Spleen	44 mSv	1171 mSv	2300 mSv	810 mSv	130 mSv
Ipsilateral lung	790 mSv	2471 mSv	582 mSv	121 mSv	80 mSv
Heart (LAD)	0.7 Gy	3.6 Gy	2.7 Gy	1.1 Gy	0.7 Gy

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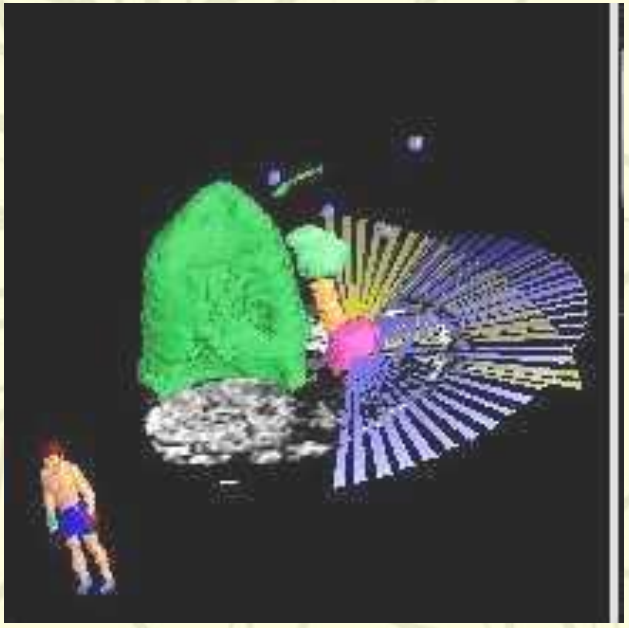
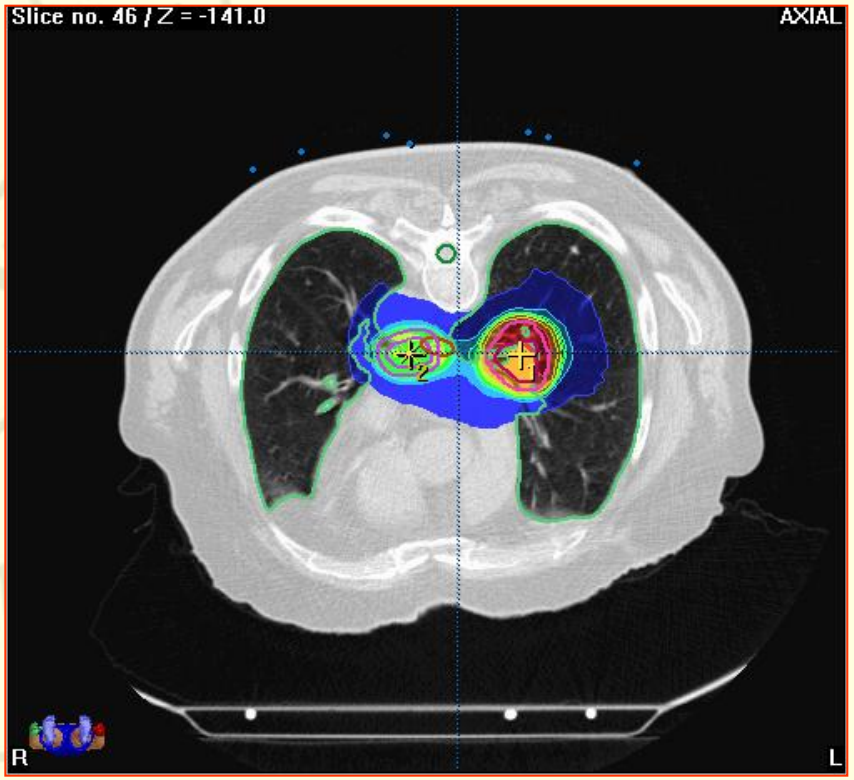
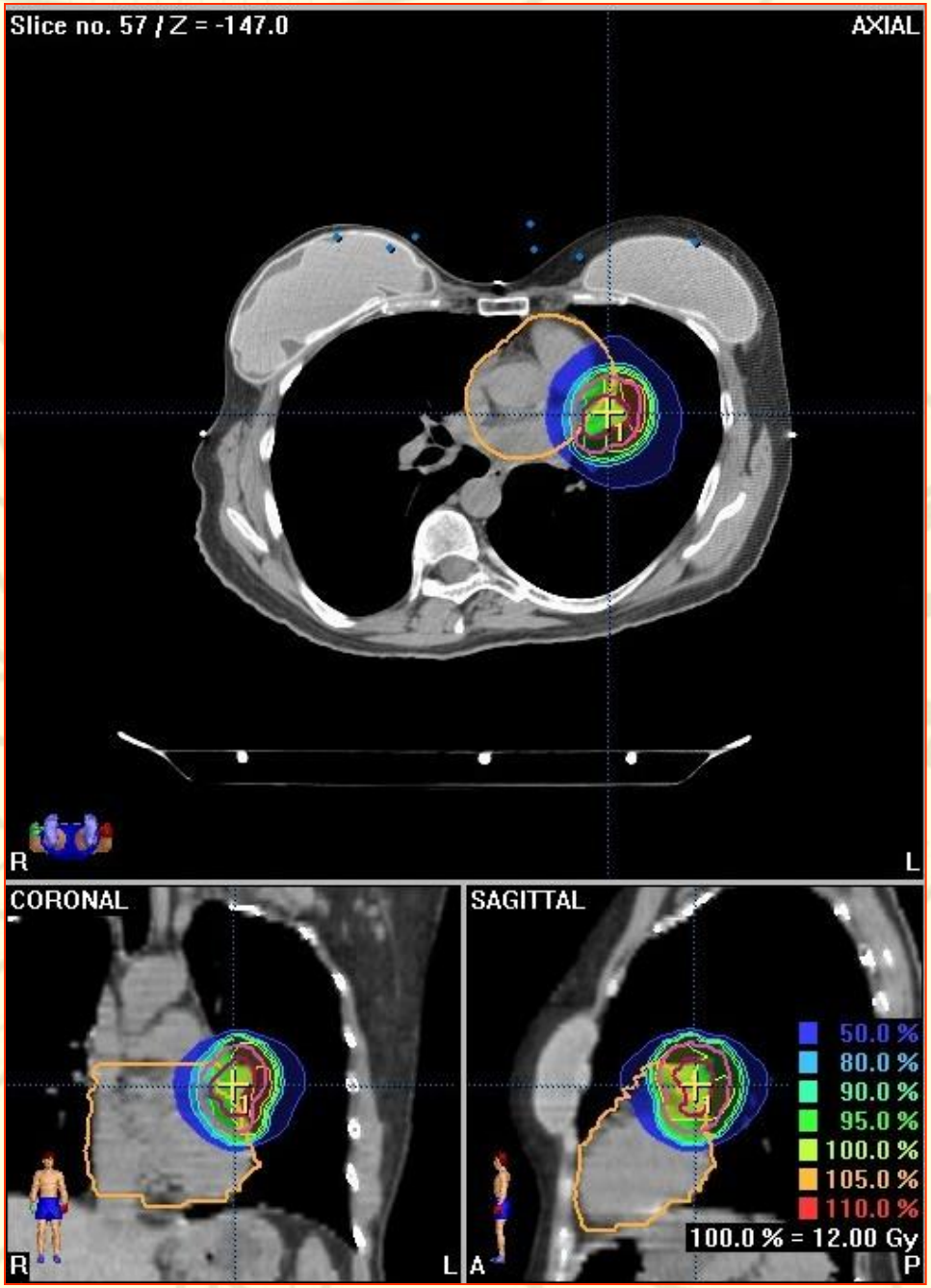
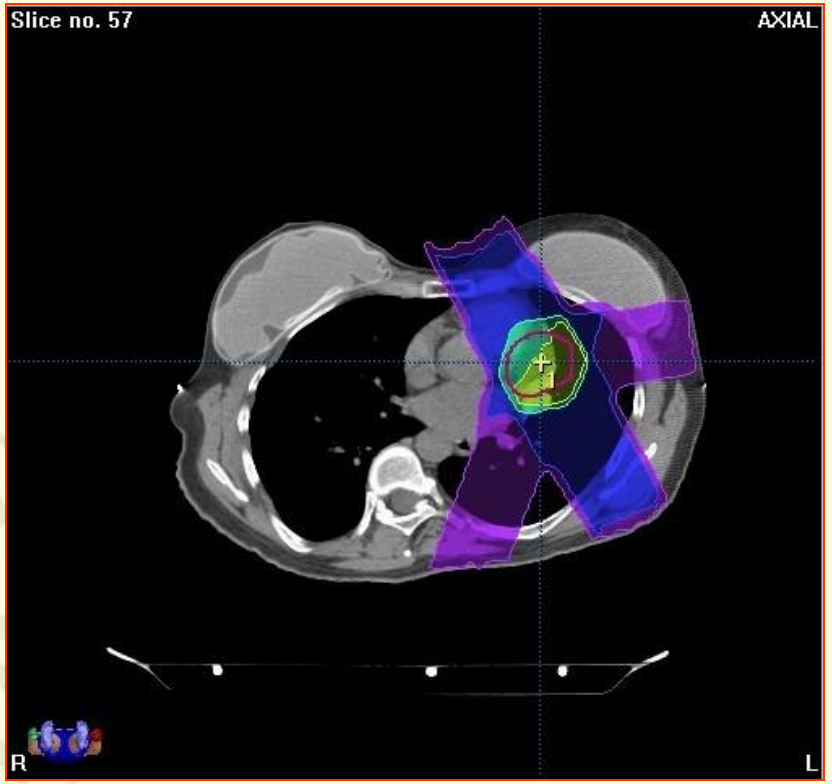
Radioterapia Stereotassica

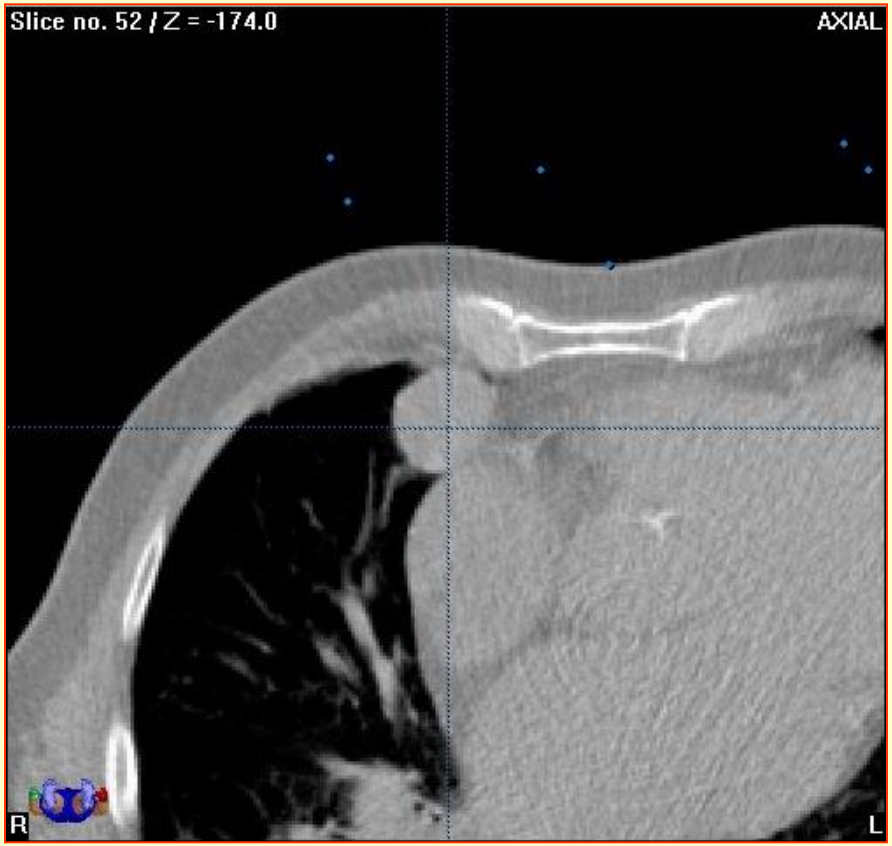
Tecnica di Radioterapia di lesioni individuate attraverso principi di localizzazione stereotassici e trattate in modo selettivo mediante fasci non coplanari di radiazioni

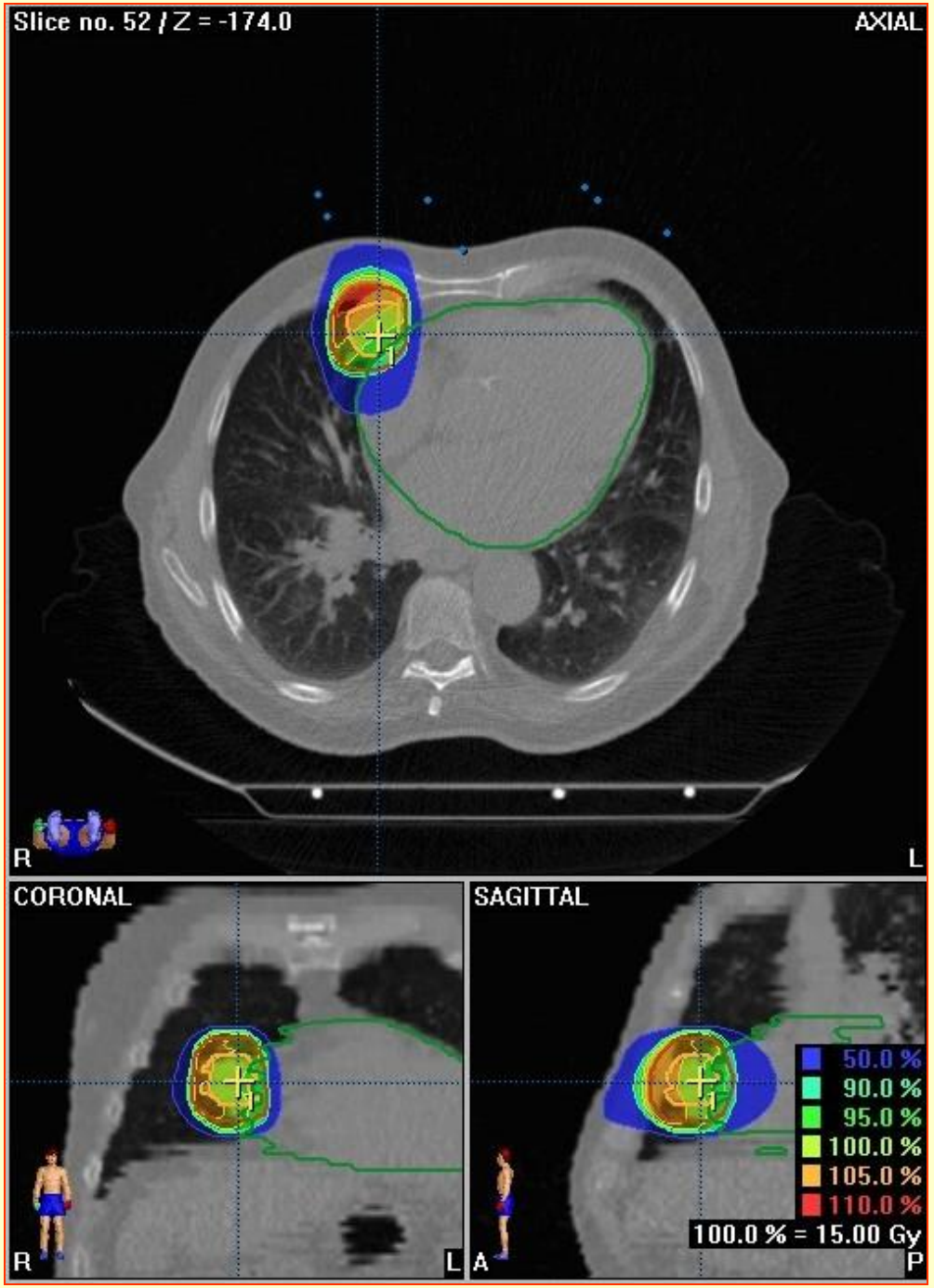





Slice no. 57 / Z = -147.0
AXIAL
R
L
CORONAL
R
L
SAGITTAL
A
P
50.0 %
80.0 %
90.0 %
95.0 %
100.0 %
105.0 %
110.0 %
100.0 % = 12.00 Gy


Slice no. 57
AXIAL
R
L


Slice no. 52 / Z = -174.0
AXIAL
R
L


Slice no. 52 / Z = -174.0
AXIAL
R
L
CORONAL
R
L
SAGITTAL
A
P
50.0 %
90.0 %
95.0 %
100.0 %
105.0 %
110.0 %
100.0 % = 15.00 Gy

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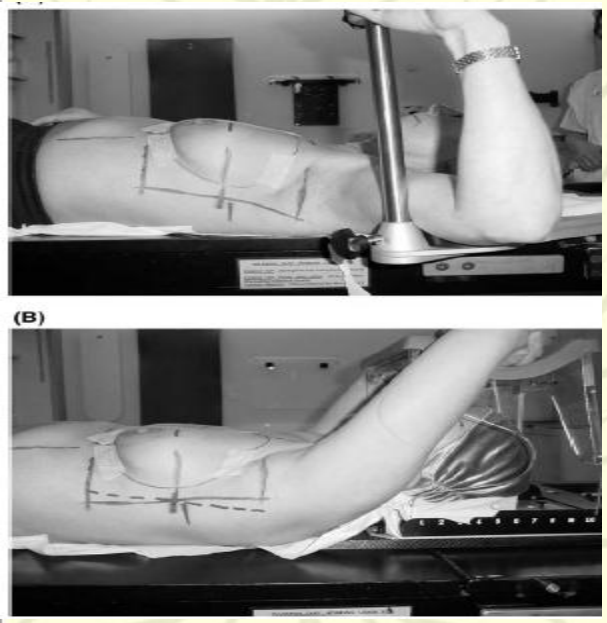
Posizionamento del paziente



Sophisticated technique but also optimum patient positioning
(Canney 1999, Canney 2001, Hurkmans, 2001)

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Prone vs. supine positioning

Heart ($n = 34$)

Mean dose (Gy)	V_{25Gy} (%)	V_{30Gy} (%)
3.51 ± 2.33	4.7 ± 4.6	4.1 ± 4.3
3.18 ± 1.31	3.6 ± 2.5	3.0 ± 2.2
0.413		

Dose to heart did not differ, but worse repositioning accuracy

Supine	
Prone	
p value	0.061

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Conclusioni

- La tossicità cardiaca da radiazioni è un evento riconosciuto
- I migliori risultati oncologici e la maggiore aspettativa di vita impongono una attenta valutazione del rischio di sequele
- I miglioramenti delle tecniche di Radioterapia possono ridurre significativamente la RIHD