Treviso, 23-24 novembre 2018

Danno cardiaco jatrogeno

Tossicità cardiaca da radioterapia

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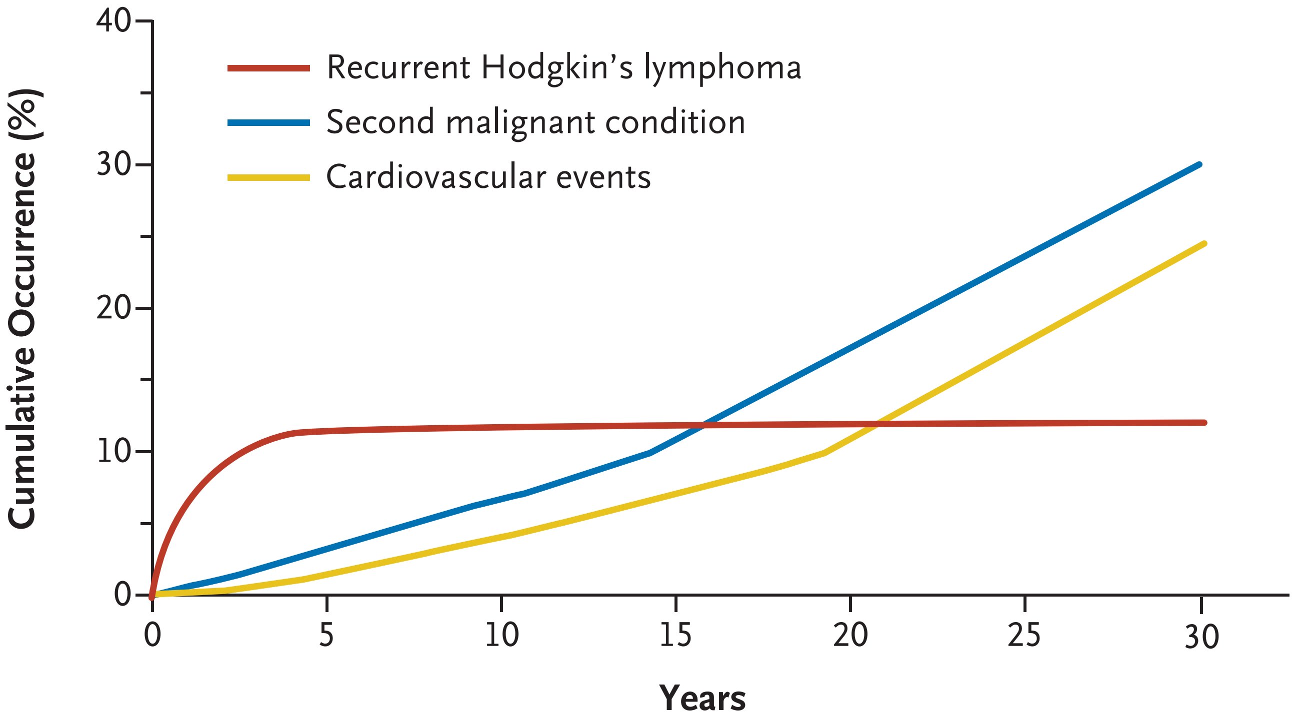
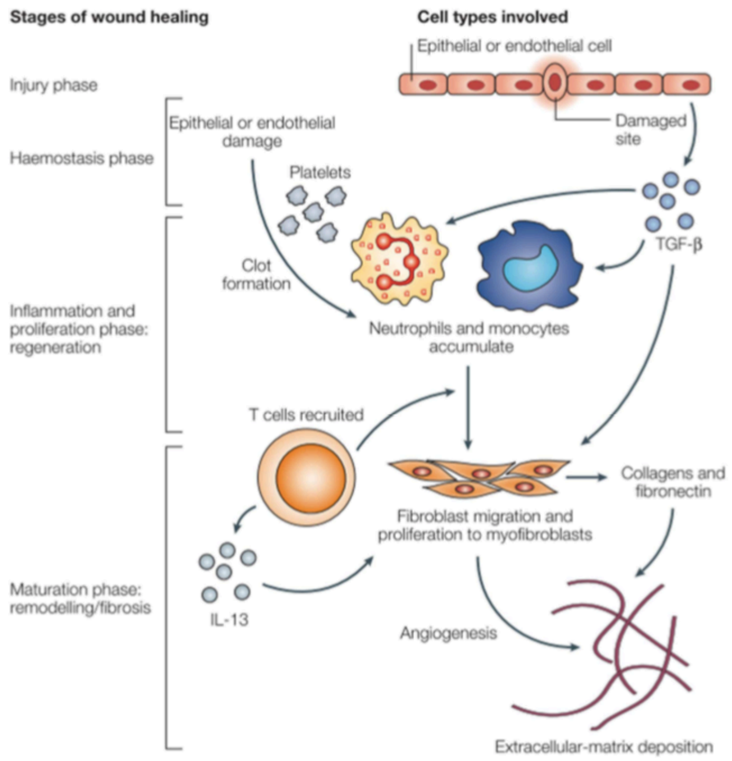
The price of success: Long term complications

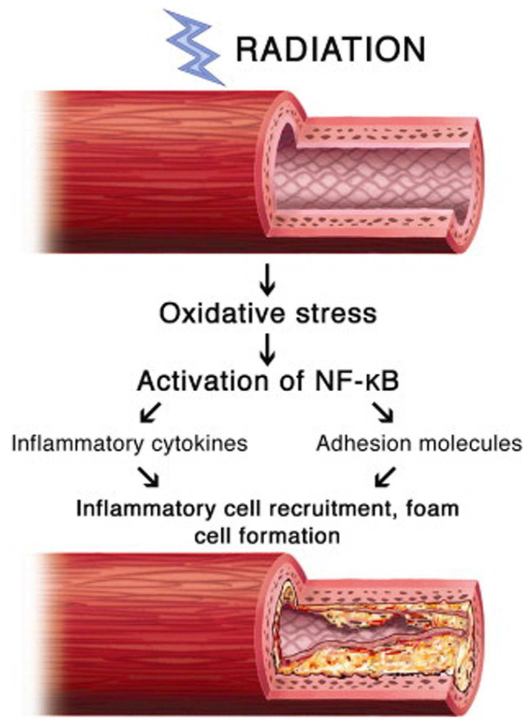


Pathogenesis of RIHD



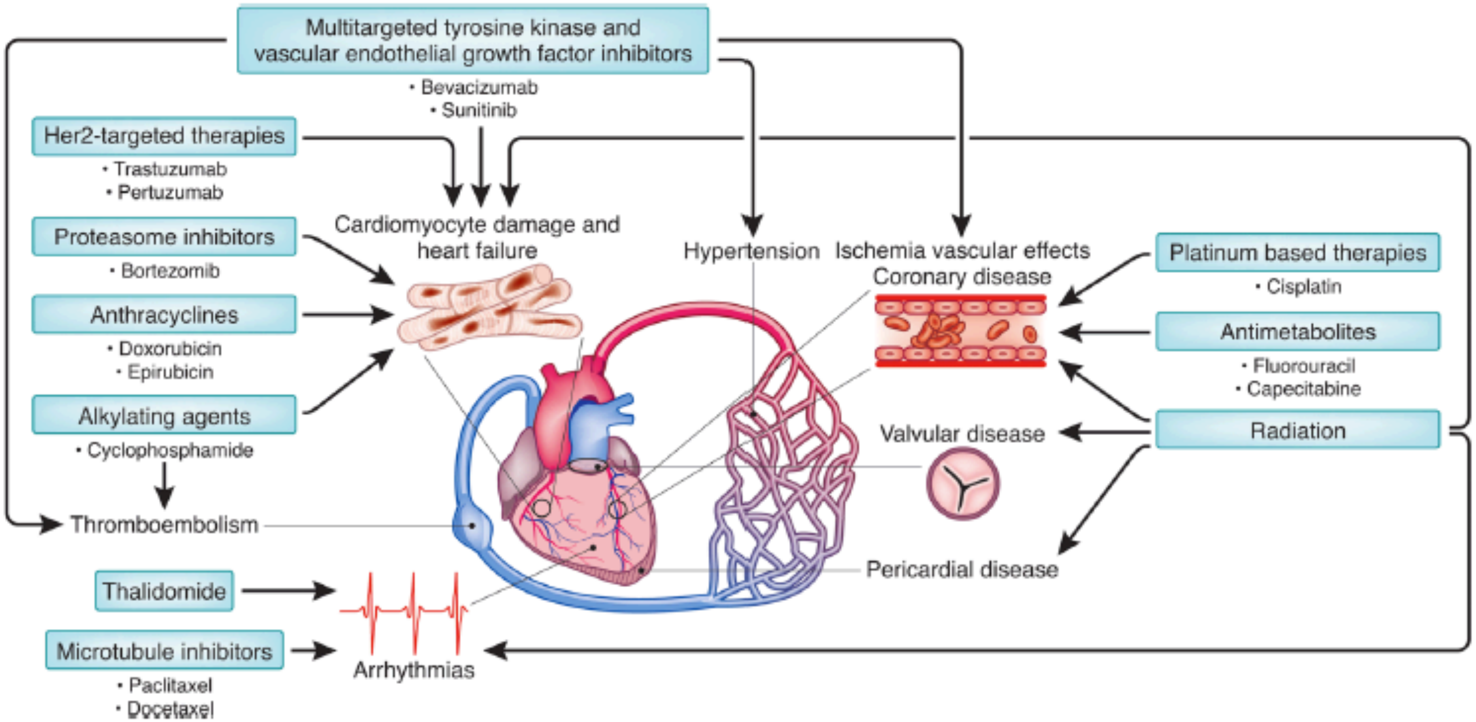
1 - Fibrosis

2 - Inflammation



Taunk N. et al. Front Oncol 2015

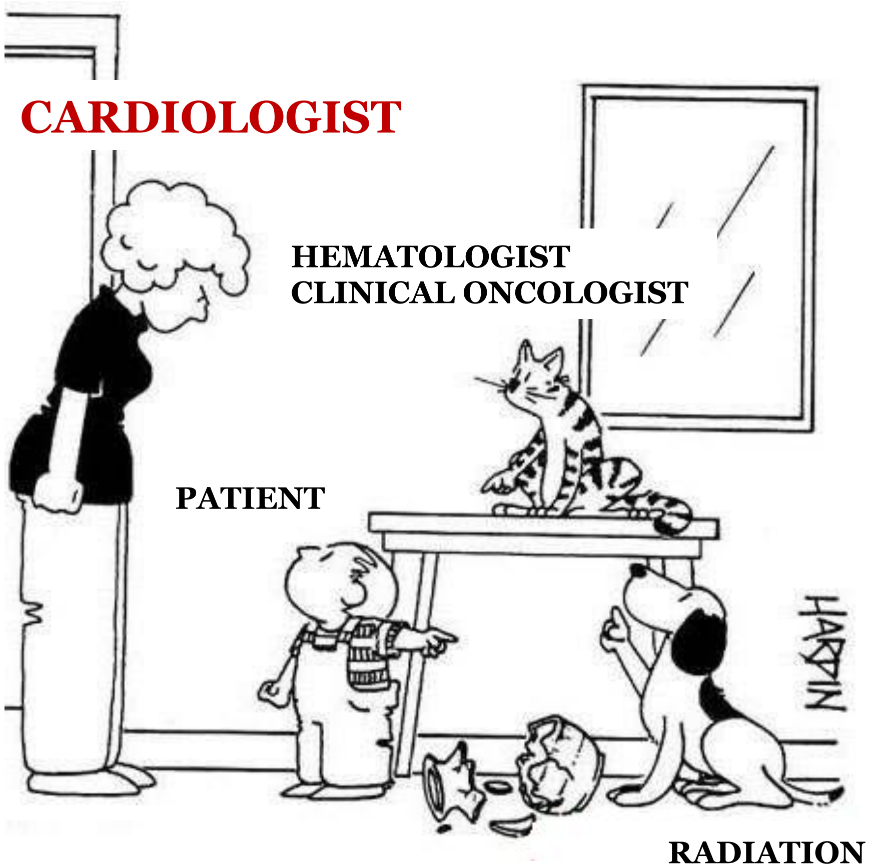
RIHD: the *"enhancing"* role of combined systemic therapies



Lenneman CG. & Sawyer DB. Circ. Res. 2016

Treatment Related Cardiac Events In Long Term Cancer Survivors…

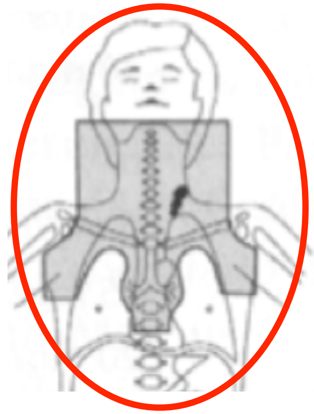
Who Is The Guilty One?



Late cardiotoxicity after treatment for Hodgkin lymphoma

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

- ✓ **1474 pts**
- ✓ **Enrollement: 1965-1995 (median follow-up 18,7 years)**
- ✓ **1241 mediastinal RT (87%)**
- ✓ **40 Gy/20 fr (RT) or 30-36 Gy (RT-CT)**



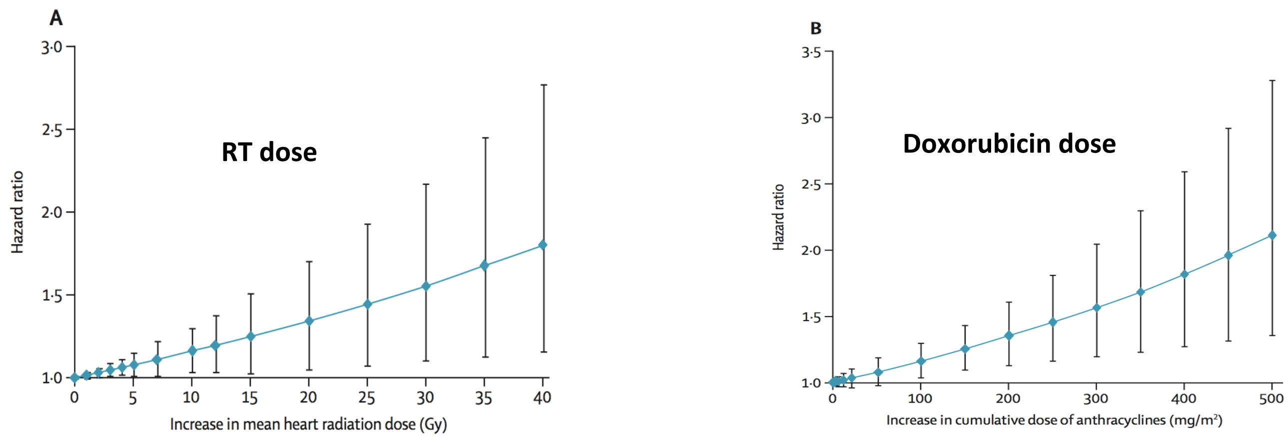
Risk factor	MI	AP	CHF*	Valvular disorders
Model 1, no. of events	102	129	82	159
Treatment, HR (95% CI)†				
Mediastinal RT (yes vs no)	2.42 (1.12-5.24)	4.85 (1.97-11.9)	7.37 (1.81-30.0)	7.01 (2.59-18.9)
Anthracycline-containing CT (yes vs no)	0.90 (0.50-1.62)	1.49 (0.89-2.49)	2.44 (1.37-4.33)	2.24 (1.40-3.59)
Cardiovascular risk factors, HR (95% CI)				
Recent smoking (yes vs no/unknown)	2.04 (1.29-3.23)	1.35 (0.85-2.16)	1.96 (1.16-3.30)	1.23 (0.80-1.88)
Hypertension (yes vs no/unknown)‡	0.52 (0.29-0.94)	0.90 (0.58-1.42)	1.07 (0.59-1.94)	1.28 (0.86-1.92)
Hypercholesterolemia (yes vs no/unknown)‡	4.12 (2.68-6.33)	4.55 (3.10-6.68)	1.48 (0.85-2.58)	1.65 (1.11-2.44)
Diabetes mellitus (yes vs no/unknown)‡	1.44 (0.73-2.83)	2.43 (1.45-4.09)	4.45 (2.54-7.81)	1.81 (1.07-3.04)
Model 2, no. of events	95	124	80	155
Treatment group, HR (95% CI)§				
Mediastinal RT only‖	1.00	1.00	1.00	1.00
Mediastinal RT + CT, no anthracyclines¶	1.17 (0.75-1.83)	0.78 (0.53-1.15)	1.33 (0.79-2.24)	0.85 (0.60-1.21)
Mediastinal RT + CT, anthracyclines#	1.00 (0.52-1.94)	1.32 (0.76-2.30)	2.81 (1.44-5.49)	2.10 (1.27-3.48)

Aleman B et al. Blood 2007;109(5):1878-1886

DEPARTMENT OF ONCOLOGY UNIVERSITY OF TURIN

Chemotherapy VS Radiotherapy… What is more toxic?

Estimated HR for cardiovascular events according to mean heart RT dose and cumulative dose of anthracyclines



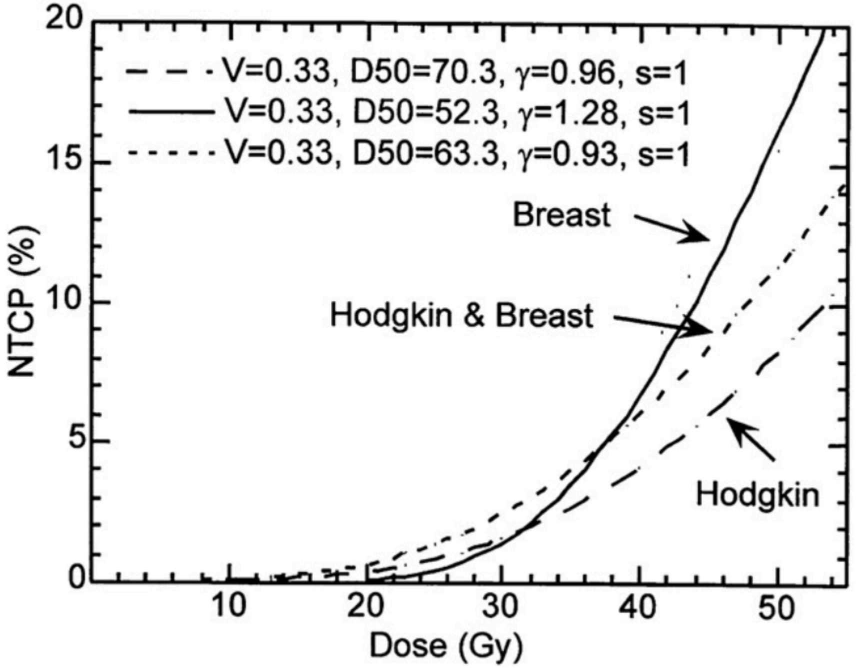
Example: an increase in **mean heart dose of 5 Gy** yields the **same excess risk** of cardiac events as an increase in cumulative **anthracycline dose of 50 mg/m2** (≈1 cycle of ABVD or R-CHOP)

WARNING

DOSE-RESPONSE RELATIONSHIP: complex and heterogeneous models

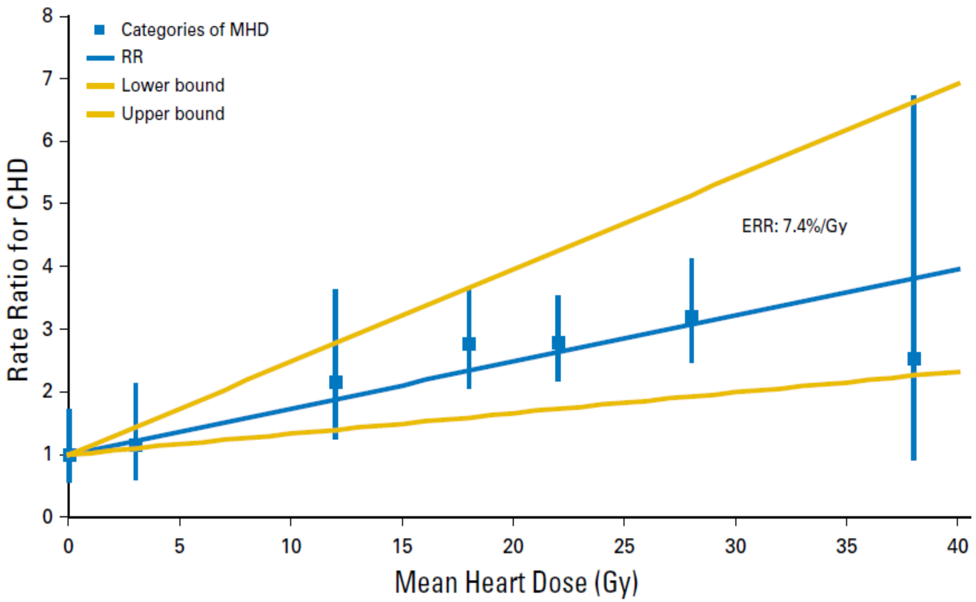
- If we consider Heart Dose, response curves are unstable and variable due to:
  - **Different radiated substructures**
  - **Concomitant cardiovascular risk factors**

Long Term Cardiac Mortality



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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



Impact of Cardiovascular risk factors

Risk Factors	RR	95% CI	p value
NONE	1	-	-
Diabetes mellitus	**1.98**	1.41 to 2.77	< 0.001
Hypercholesterolemia	**2.08**	1.60 to 2.72	< 0.001
Hypertension	**1.52**	1.18 to 1.96	< 0.001
>1 risk factors	**2.51**	1.84 to 3.44	< 0.001

van Nimwegen et al. JCO 2016

Prevention Of Treatment Related Cardiac Events Is Pivotal, So…
How Can We Prevent Radiation-Induced Cardiac Complications ?

PRIMARY PREVENTION

- ❑ Avoidance/reduction of cardiotoxic treatments
- ❑ Technical improvement
- ❑ Management of cardiac risk factors
- ❑ Cardioprotective drugs

SECONDARY PREVENTION
(early diagnosis)

❑ Diagnostic tools

1. Biomarkers *(Troponine, NTproBNP, miRNA)*
2. Echocardiography
3. Cardiac MRI
4. Coronary angiography CT scan

1

PROSPECTIVE AND DETAILED CONTOURING OF THE HEART STRUCTURES

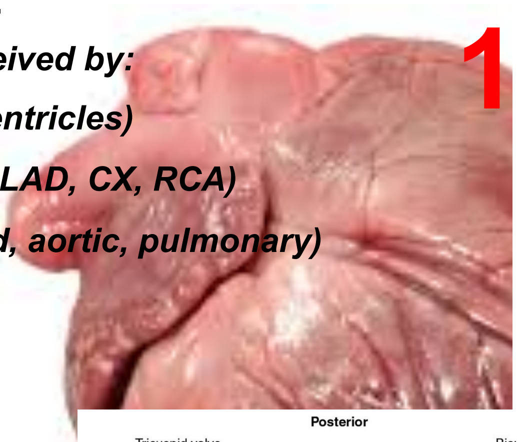
Modern concept

Estimation of the dose received by:

1) ***Chambers (atria and ventricles)***
2) ***Coronary arteries (LM, LAD, CX, RCA)***
3) ***Valves (mitral, tricuspid, aortic, pulmonary)***

Old concept

Estimation of Whole Heart dose



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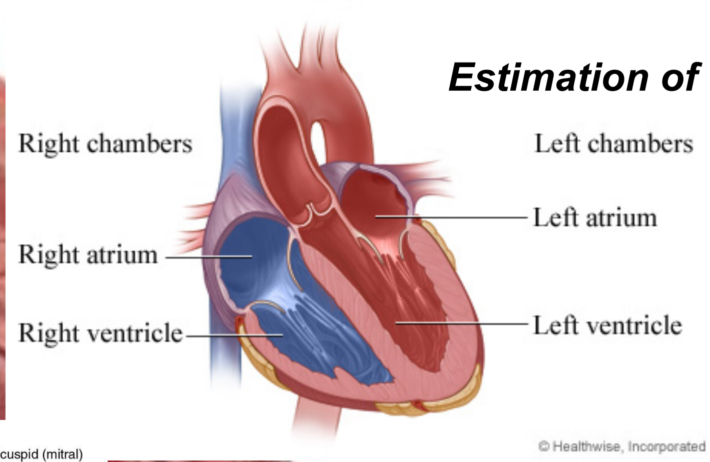

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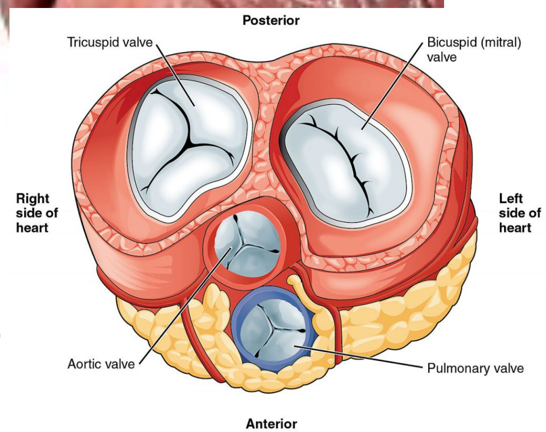

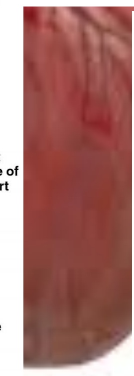

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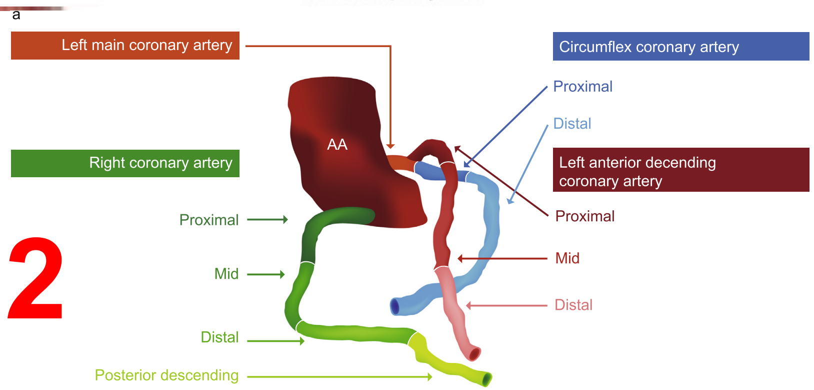
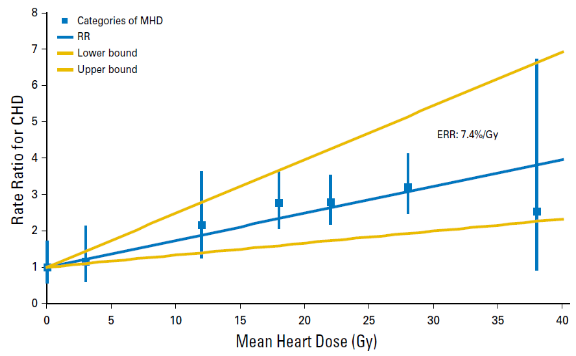


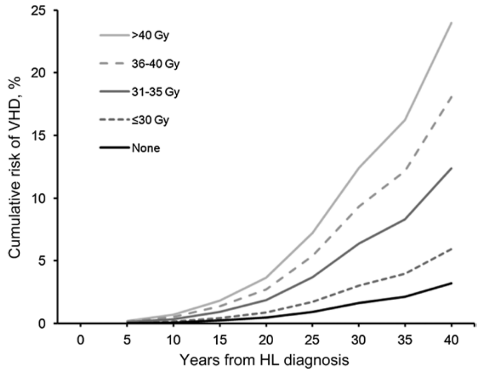
Correlation between heart (substructures) dose and cardiac events

MHD
and development of CAD



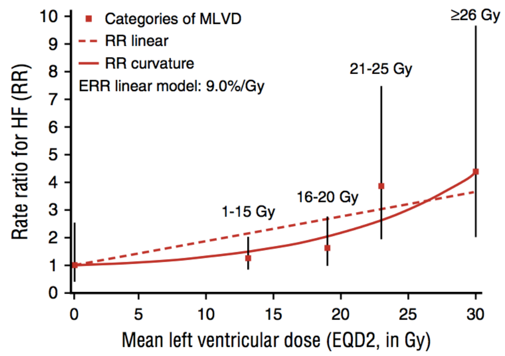
van Nimwegen et al. JCO 2016

Valvular dose
and development of VHD



Cutter et al. JNCI 2015

MLVD
and development of CHF

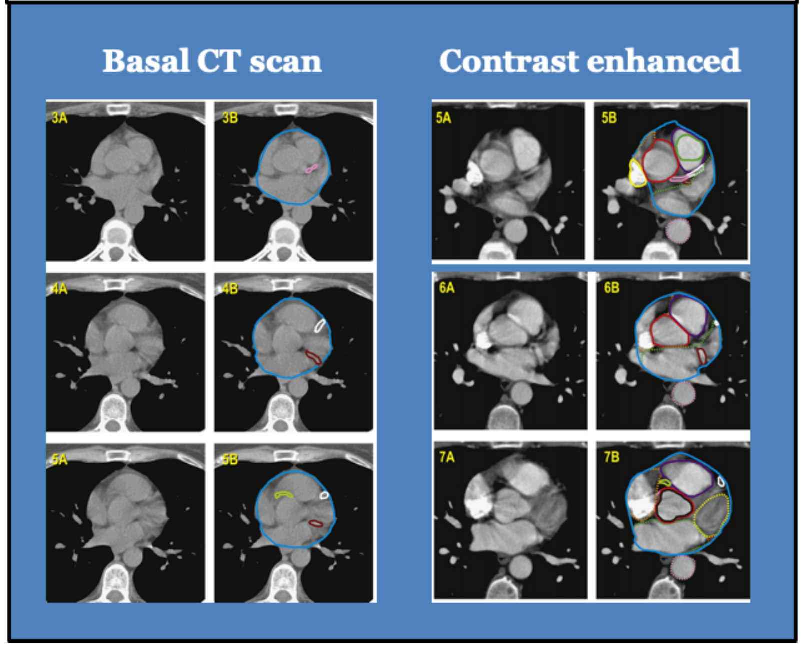


van Nimwegen et al. Blood 2017

CONTOURING OF THE HEART STRUCTURES

CLINICAL INVESTIGATION — Breast

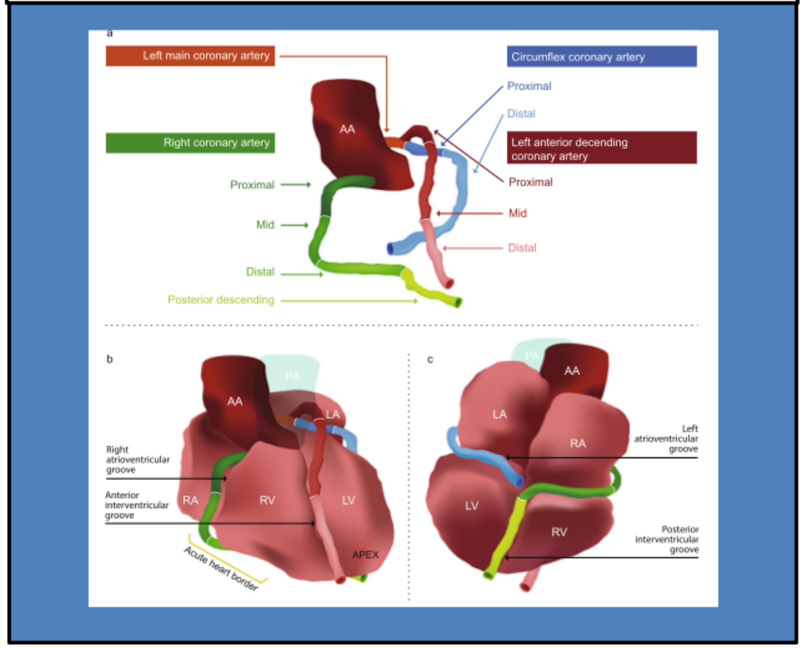
DEVELOPMENT AND VALIDATION OF A HEART ATLAS TO STUDY CARDIAC EXPOSURE TO RADIATION FOLLOWING TREATMENT FOR BREAST CANCER



Feng M et al. IJROBP 2011

A cardiac contouring atlas for radiotherapy

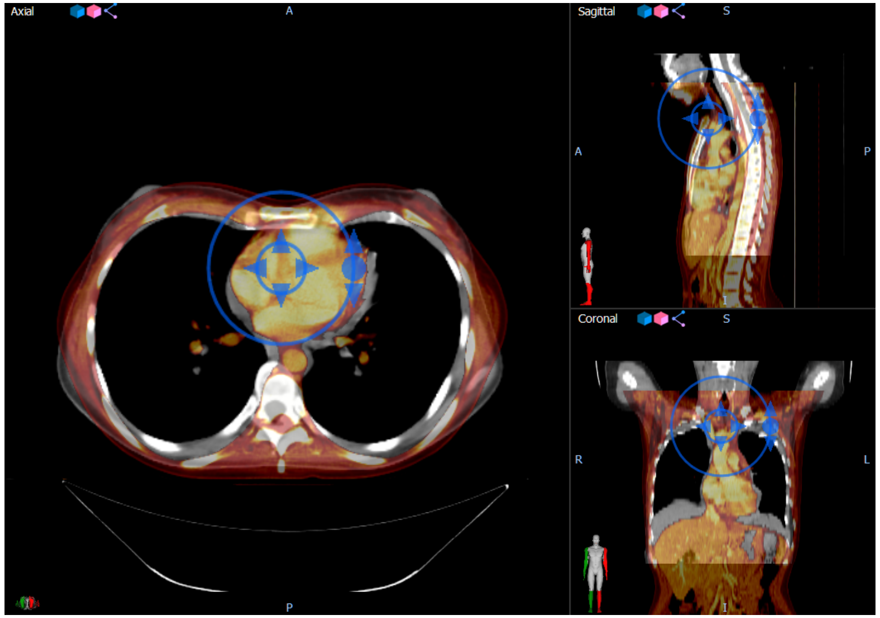
Frances Duane [a,b,*], Marianne C. Aznar [a], Freddie Bartlett [c], David J. Cutter [a], Sarah C. Darby [a], Reshma Jagsi [d], Ebbe L. Lorenzen [e], Orla McArdle [f], Paul McGale [a], Saul Myerson [g], Kazem Rahimi [h], Sindu Vivekanandan [i], Samantha Warren [j], Carolyn W. Taylor [a]



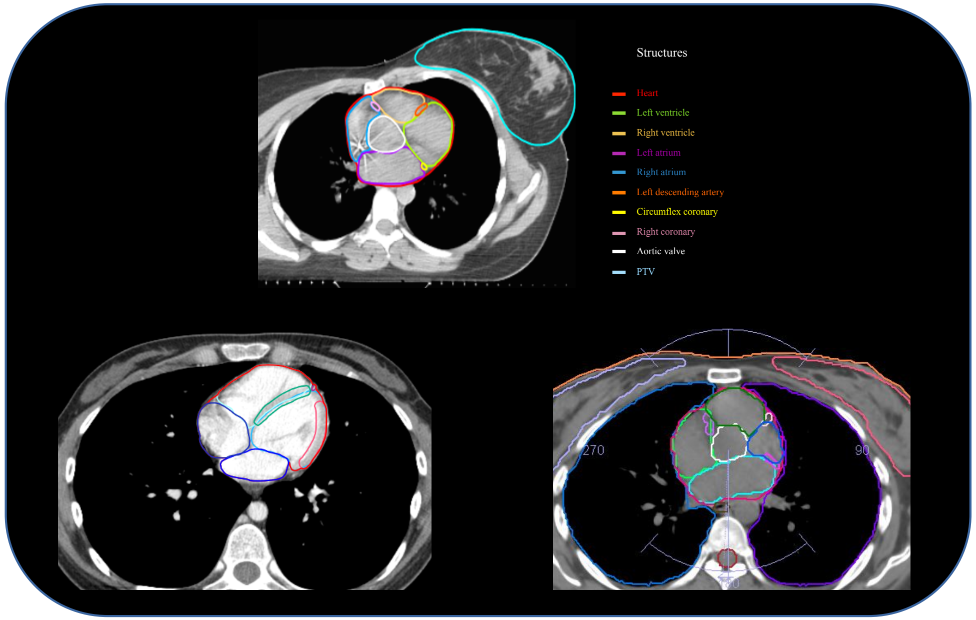
Duane F. et al. Radiother Oncol 2018

TREATMENT PLANNING

1 – Deformable registration

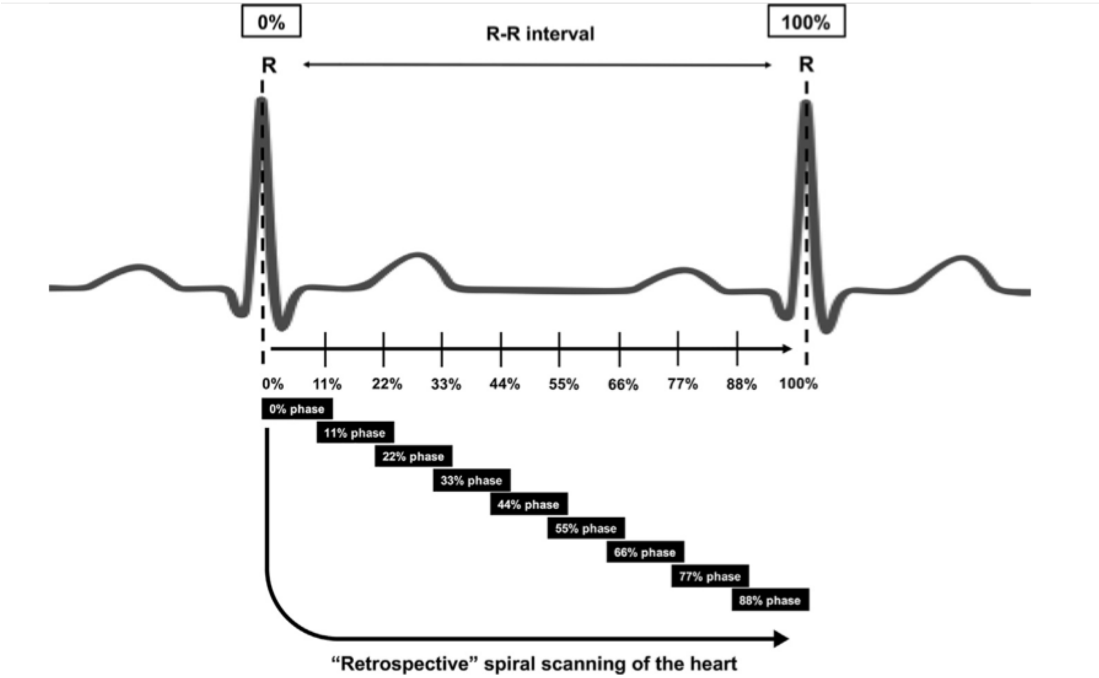


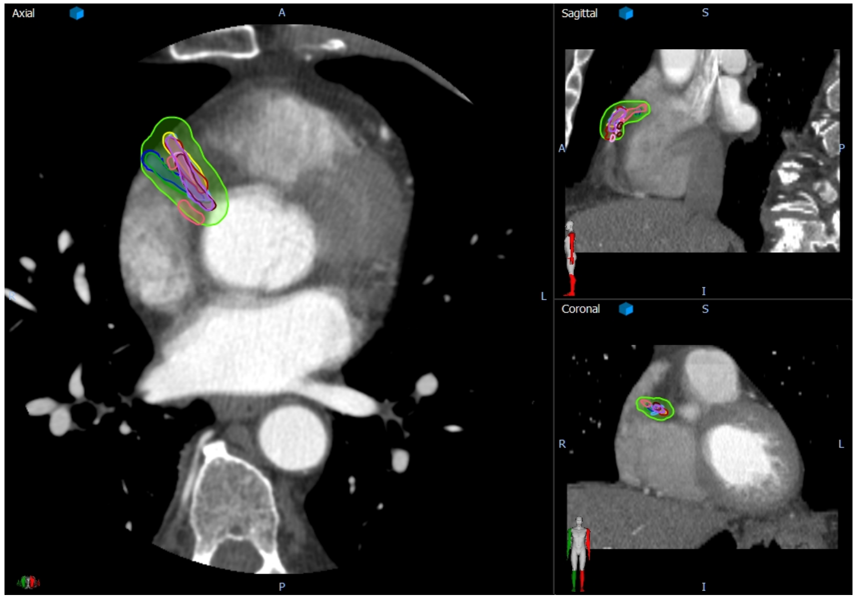
2 – Accurate contouring of cardiac structures



Plan optimization for mediastinal radiotherapy: Estimation of coronary arteries motion with ECG-gated cardiac imaging and creation of compensatory expansion margins

Mario Levis [a], Viola De Luca [a], Christian Fiandra [a], Simona Veglia [b], Antonella Fava [c], Marco Gatti [d], Mauro Giorgi [c], Sara Bartoncini [a], Federica Cadoni [a], Domenica Garabello [b], Riccardo Ragona [e], Andrea Riccardo Filippi [e,*], Umberto Ricardi [a,e]





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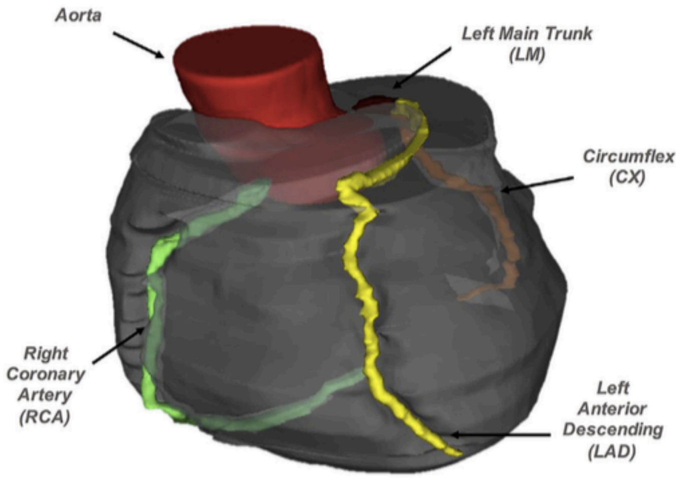


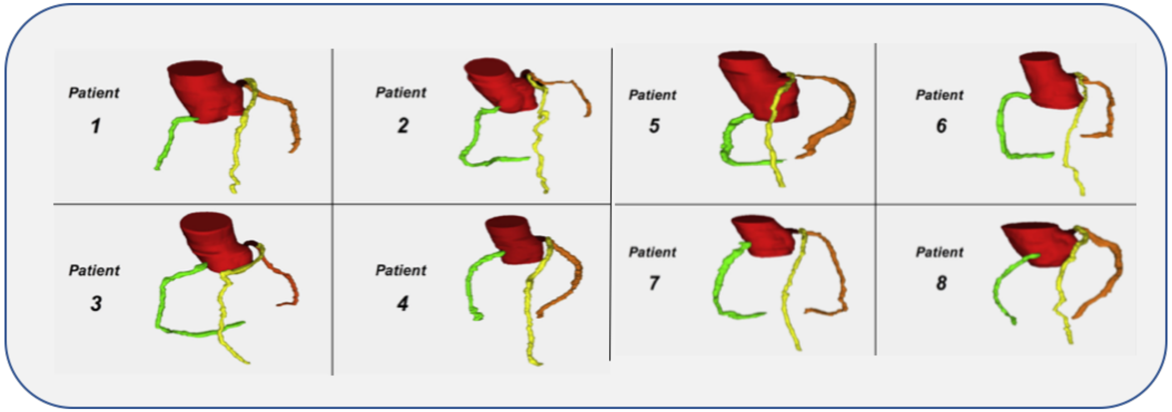


Table 1
Mean coronary arteries displacements evaluated with the McKenzie–van Herk formula [15] for organs at risk (mPRV = 1.3 * Σ + 0.5 * σ), for the overall population of 8 patients.

Coronary artery	Displacement (mm)			Suggested PRV margin (mm)
	Left-Right (X) Σ and σ	Cranio-caudal (Y) Σ and σ	Antero-posterior (Z) Σ and σ	
Left main trunk (LM)	3.6 0.215 and 0.169	2.7 0.143 and 0.177	2.7 0.143 and 0.162	**3**
Left anterior descending (LAD)	2.6 0.143 and 0.154	5.0 0.228 and 0.395	6.8 0.413 and 0.291	**5**
Circumflex (CX)	3.5 0.196 and 0.179	4.5 0.239 and 0.283	3.7 0.183 and 0.256	**4**
Right (RCA)	3.6 0.169 and 0.276	4.6 0.232 and 0.324	6.9 0.355 and 0.446	**5**

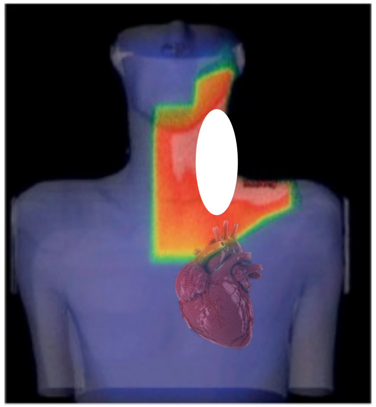
2

“CHOOSING WISELY”… RT OFFER TAILORED TO THE PATIENTS BY ADOPTING COMPARATIVE PLANNING

Evolution in the definition of RT volumes for lymphoma patients

Mantle field
<u>1980-1990</u>

Involved field
<u>1990-2010</u>



Volume treated on the basis of anatomical borders

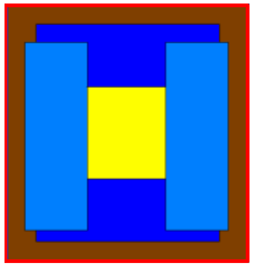
Involved site - Involved node
<u>2010-nowadays</u>

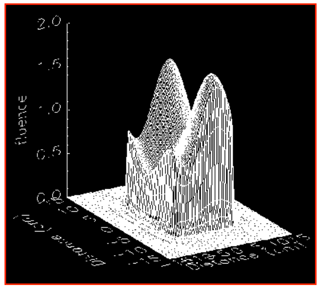
Targets of treatment are only lymph nodes and/or extranodal sites involved at baseline

THE CONFORMALITY CONTINUUM

1980s	Late 1990s	2000s	2010s	2020s
2D	3D-CRT	IMRT/VMAT/TOMO	IGRT	

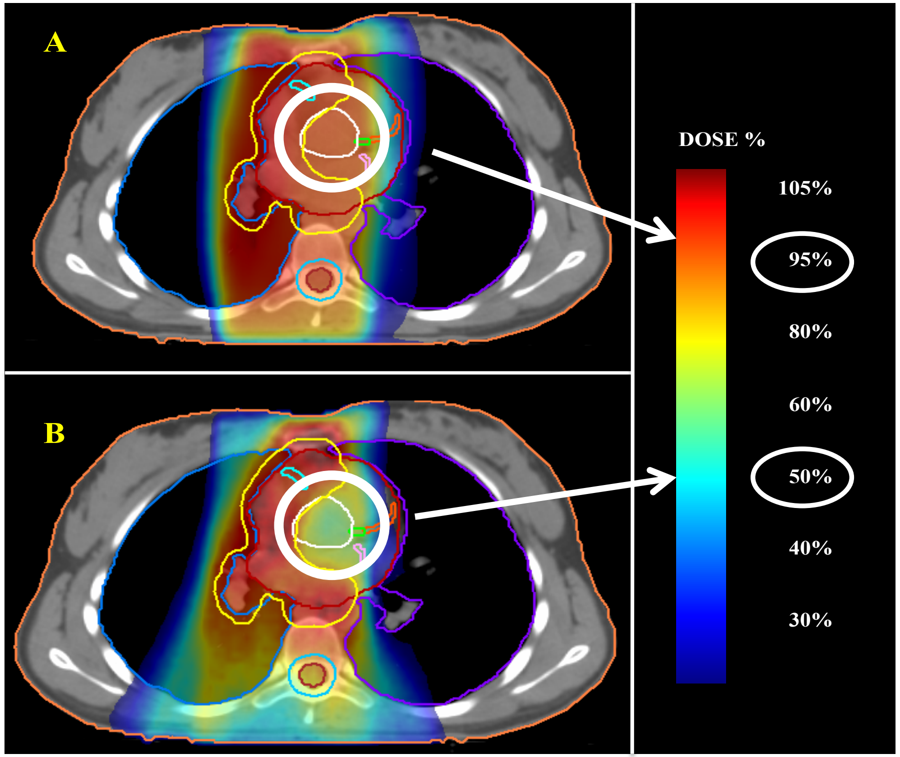
TREND – Improving Precision





To be continued…

MODERN TECHNIQUES PLAY A MAJOR ROLE SINCE WHOLE HEART DOSE CANNOT LONGER BE ENOUGH…

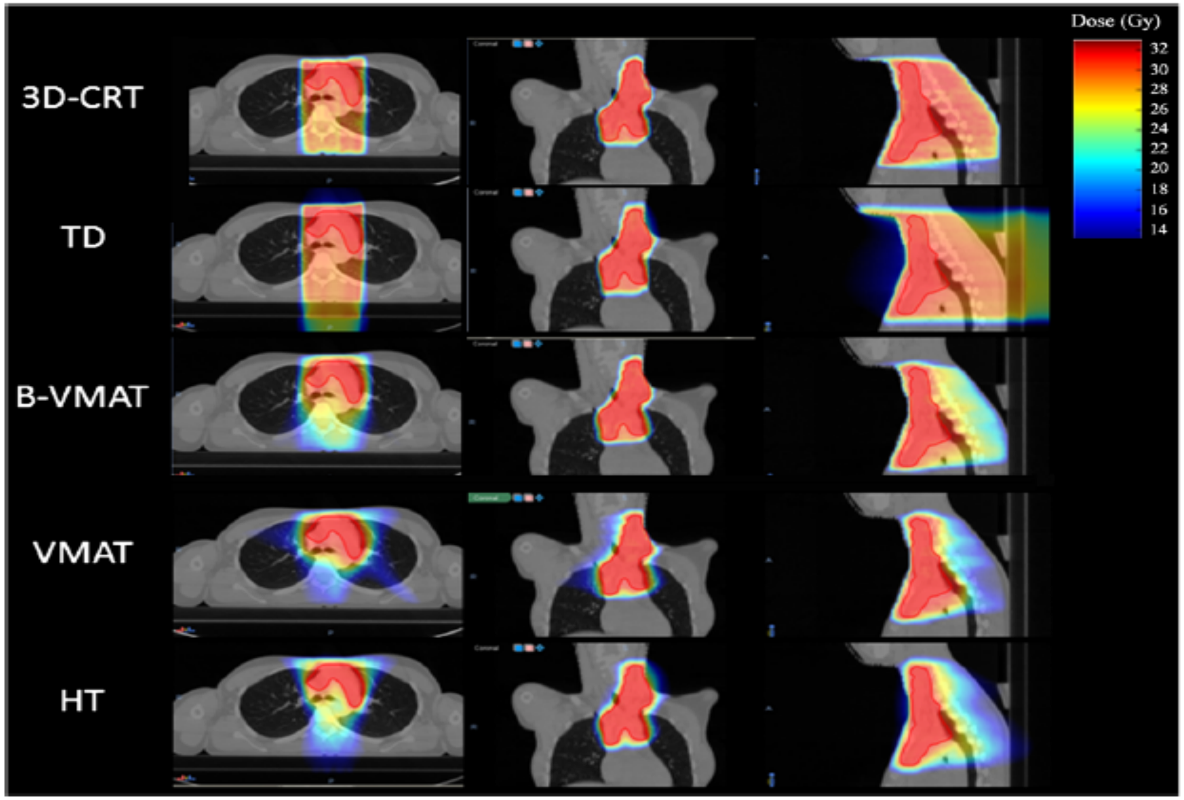


Mean Heart dose similar for 3DCRT and VMAT but…

With VMAT we achieve a better sparing of:

- **aortic valve**
- **Left main**
- **Proximal left descending**
- **Proximal circumflex**

IMRT in HL: which technique is preferable ?



Fiandra et al, Radiation Oncology 2012

Which technique is preferable?

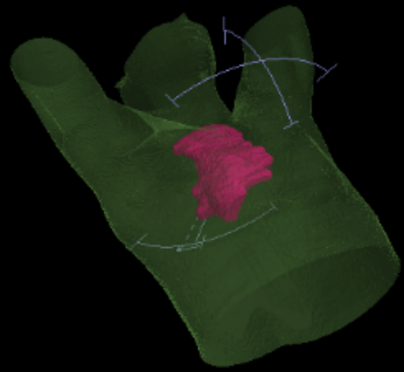
- ***There is no single proven best planning and delivery RT technique***
- ***No two lymphomas are the same*** with regard to localization and extent of disease
- The decision should be made at the ***individual patient level***, depending on:
  - Age
  - Gender
  - Comorbidities and risk factors for other diseases
  - Dosimetric data adapted for lymphoma patients

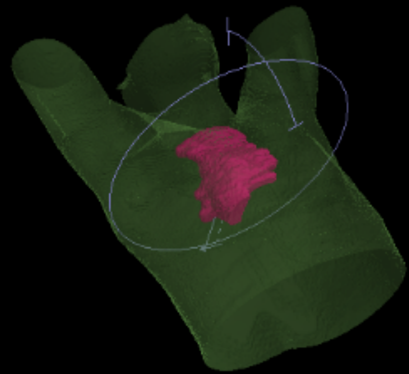
A

"Butterfly" VMAT (B-VMAT)

2 coplanar arcs of 60°
- 1 anterior
- 1posterior

1 no-coplanar arc of 60°



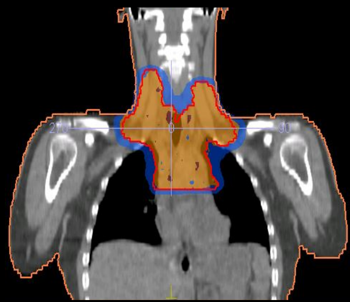


B

Full Arc "Bufferfly" VMAT (FaB-VMAT)

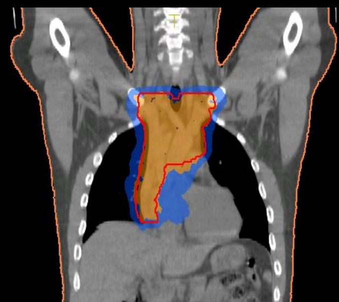
1 coplanar arc of 360°
1 no-coplanar arc of 60°

Disease Presentation



A – mediastinum + neck (10 patients)

B – mediastinum + axilla (10 patients)



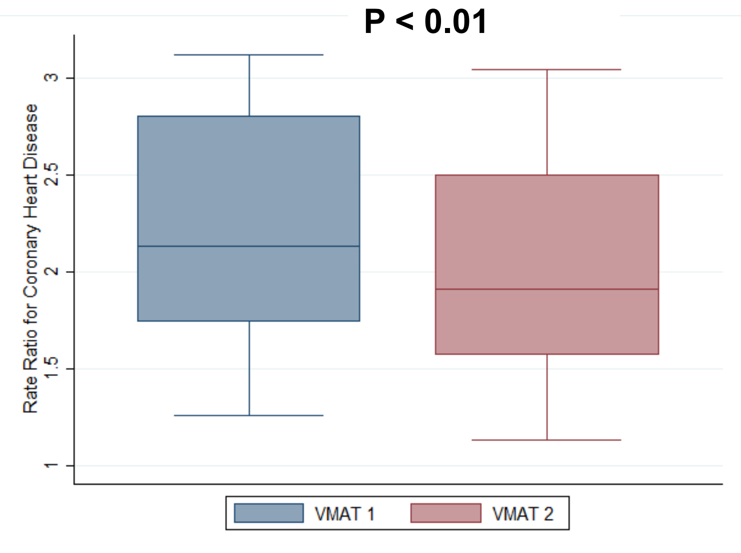
C – mediastinum alone (10 patients)

RESULTS (Heart structures)

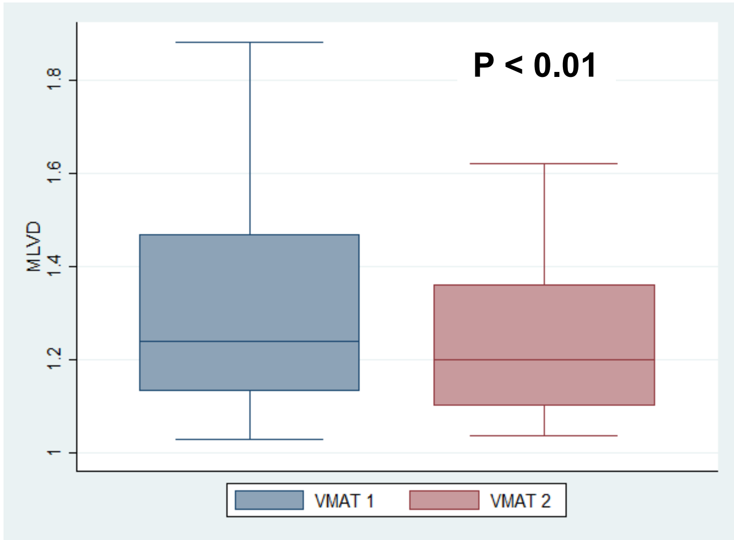
	STRUCTURE	PARAMETERS	B-VMAT (VMAT1)	FA (VMAT2)	p-value
	CORONARY ARTERIES				
	1) LEFT MAIN CORONARY	DMEAN (Gy)	19,5 ± 7,7	15,9 ± 7,5	**0,0001**
		DMAX (Gy)	25,8 ± 5,9	21,6 ± 7,4	**0,0001**
	2) LEFT ANTERIOR DESCENDING	DMEAN (Gy)	15,6 ± 9,0	13,2 ± 8,9	**0,0001**
		DMAX (Gy)	26,2 ± 8,5	21,9 ± 10,6	**0,0001**
In favor of FA-VMAT	3) LEFT CIRCUMFLEX	DMEAN (Gy)	14,0 ± 8,6	10,7 ± 7,8	**0,0001**
		DMAX (Gy)	22,7 ± 7,9	17,9 ± 9,0	**0,0001**
	4) RIGHT CORONARY	DMEAN (Gy)	17,0 ± 11,4	15,8 ± 11,6	**0,005**
		DMAX (Gy)	23,1 ± 11,5	20,9 ± 12,6	**0,006**
	5) CORONARY SUM (OVERALL)	DMEAN (Gy)	16.1 ± 9,3	13.5 ± 8,9	**0,0001**
	CHAMBERS				
	1) LEFT ATRIUM	DMEAN (Gy)	13,10 ± 6,73	11,11 ± 6,56	0,364
		DMAX (Gy)	29,25 ± 6,04	28,40 ± 7,13	0,775
In favor of FA-VMAT	2) LEFT VENTRICLE	DMEAN (Gy)	4,2 ± 4,7	3,4 ± 3,7	**0,007**
		DMAX (Gy)	25,6 ± 9,8	21,9 ± 11,1	**0,0001**
	3) RIGHT ATRIUM	DMEAN (Gy)	12,58 ± 7,29	11,9 ± 7,69	0,095
		DMAX (Gy)	30,76 ± 5,46	30,74 ± 5,34	0,899
	4) RIGHT VENTRICLE	DMEAN (Gy)	7,3 ± 6,2	7,0 ± 6,1	0,17
		DMAX (Gy)	31,1 ± 5,7	30,2 ± 6,9	0,08
	VALVES				
In favor of FA-VMAT	1) AORTIC VALVE	DMEAN (Gy)	15,7 ± 9,0	13,2 ± 8,7	**0,0004**
		DMAX (Gy)	23,3 ± 9,1	22,8 ± 10,0	0,42
	2) PULMONIC VALVE	DMEAN (Gy)	19,91 ± 7,75	18,69 ± 7,92	0,153
		DMAX (Gy)	28,35 ± 6,42	26,77 ± 7,06	0,135
	3) MITRAL VALVE	DMEAN (Gy)	8,97 ± 4,93	8,76 ± 7,48	0,939
		DMAX (Gy)	19,94 ± 6,02	14,95 ± 10,37	0,232
	4) TRICUSPID VALVE	DMEAN (Gy)	9,74 ± 8,5	9,40 ± 9,70	0,809
		DMAX (Gy)	16,86 ± 10,82	15,02 ± 11,7	0,068

Long term cardiac risk

CAD risk



CHF risk



RESULTS (PTV and OARs)

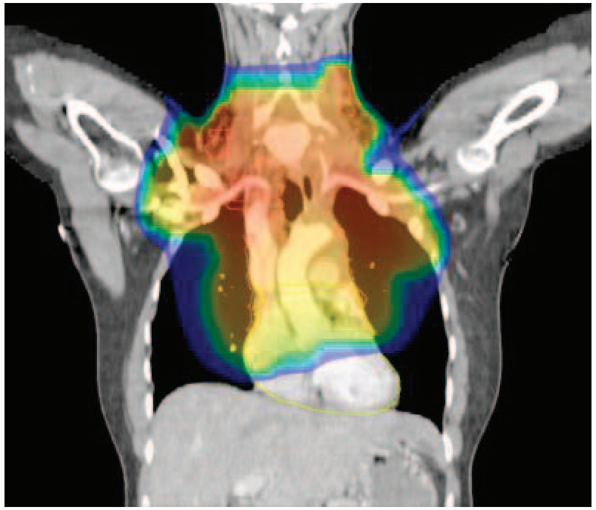
	STRUCTURE	PARAMETERS	B-VMAT (VMAT1)	FaB (VMAT2)	p-value
	PTV	DMEAN (Gy)	30,4 ± 1,9	30,4 ± 1,8	0,694
		DMAX (Gy)	34,7 ± 2,1	34,6 ± 1,8	0,545
		V95 (%)	5,7 ± 5,2	5,4 ± 2,9	0,8
		V107(%)	2,0 ± 1,0	2,0 ± 1,5	0,875
In favor of FA-VMAT →	**LUNG**	D MEAN (Gy)	7,5 ± 1,9	7,5 ± 1,7	0,954
		DMAX (Gy)	33,4 ± 2,2	33,7 ± 1,9	0,407
		V5 (%)	39,8 ± 9,5	41,1 ± 7,4	0,157
		V10 (%)	27,9 ± 7,3	27,5 ± 7,1	0,393
		V20 (%)	15,4 ± 5,9	14,4 ± 5,4	**0,008**
In favor of B-VMAT →	**BREAST**	D MEAN (Gy)	2,8 ± 3,0	3,5 ± 2,7	**0,033**
		DMAX (Gy)	27,2 ± 9,5	27,7 ± 9,4	0,53
		V4 (%)	16,6 ± 16,1	22,2 ± 15,5	**0,041**
In favor of FA-VMAT →	**HEART**	D MEAN (Gy)	7,6 ± 5,1	6,9 ± 4,8	**0,0028**
		DMAX (Gy)	32,8 ± 3,6	42,5 ± 55	0,34

3

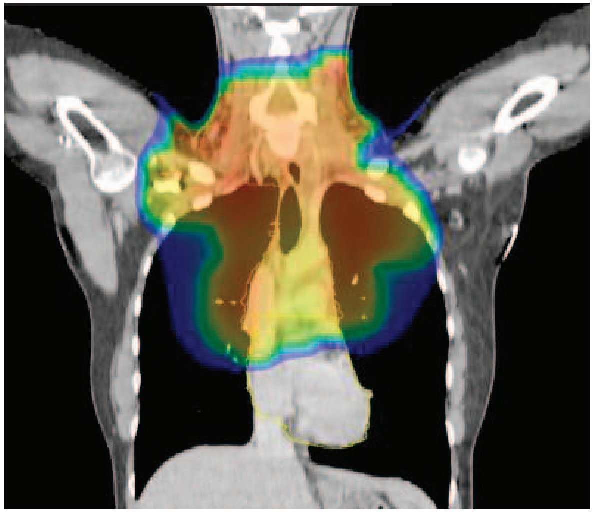
RESPIRATORY GATING (DIBH) INTEGRATED TO MODERN TECHNIQUES

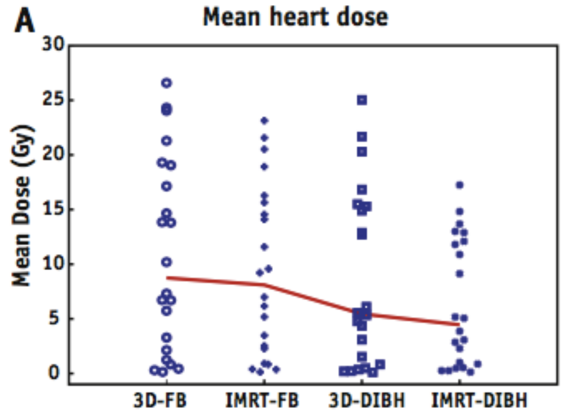
Minimizing Late Effects for Patients With Mediastinal Hodgkin Lymphoma: Deep Inspiration Breath-Hold, IMRT, or Both?

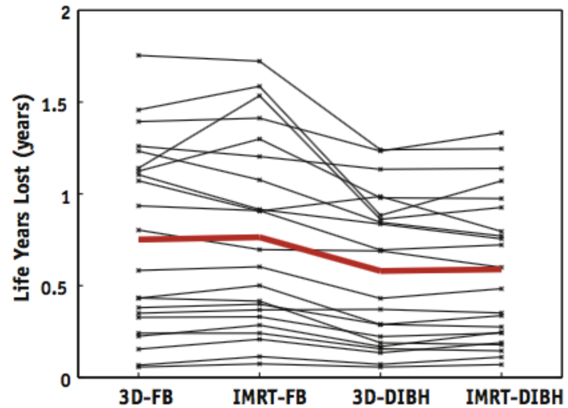
FREE BREATHING



DIBH





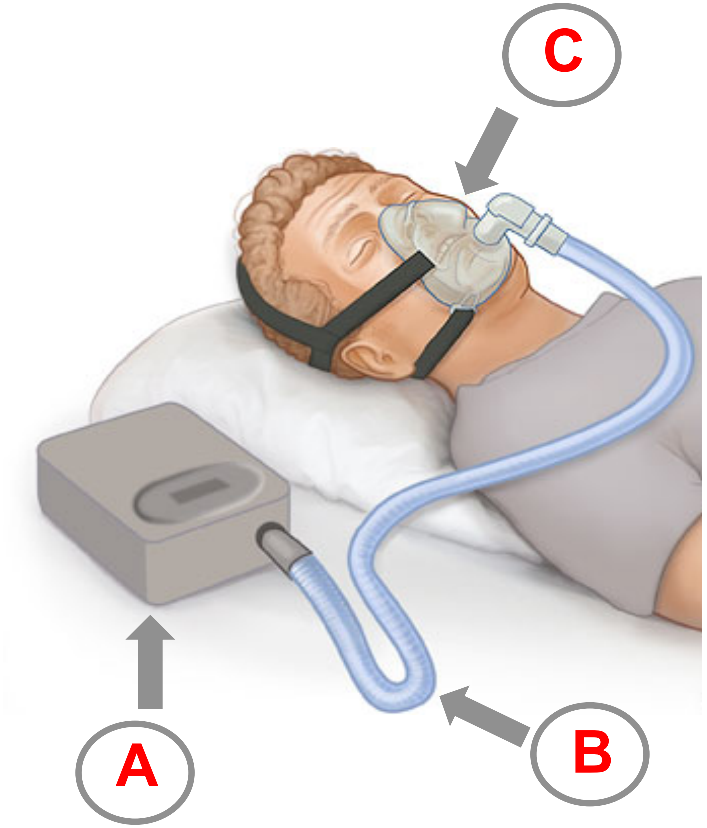


Aznar MC et al. IJROBP 2015

Continuous Positive Airway Pressure (C-PAP):

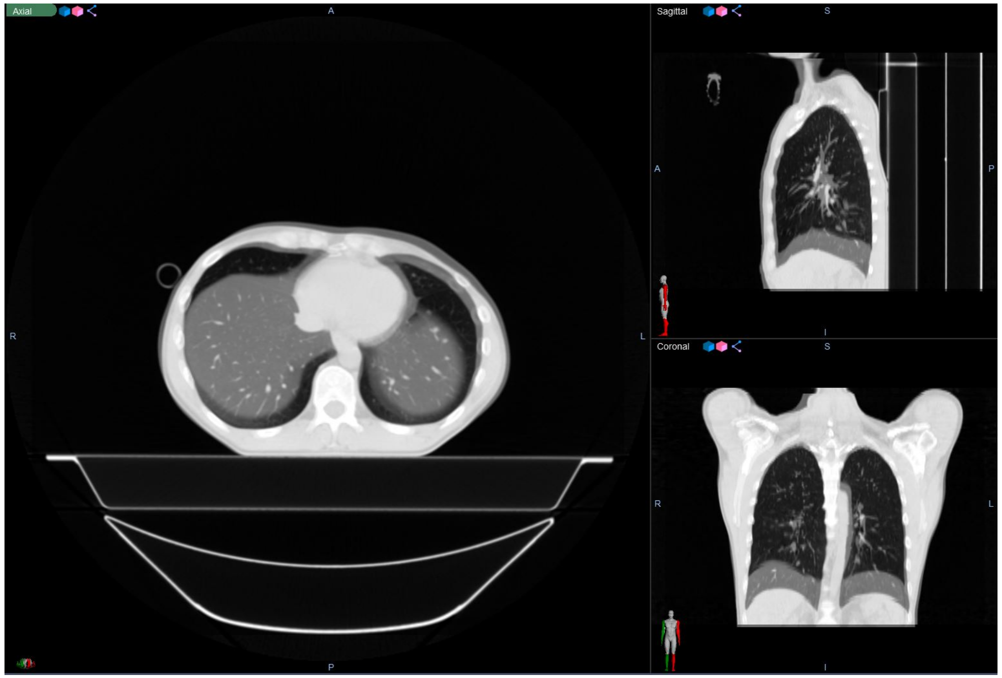
A valuable alternative way for "respiratory gating"?

- ❑ CPAP has long been safely used in patients with respiratory failure, chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSAS) to maintain airway patency.
- ❑ It provides a constant stream of pressurized air to the upper airways and lungs. The physiologic effects expected during CPAP are hyperinflation of the lungs, stabilization and flattening of the diaphragm, and decrease in tidal volume.
- ❑ **Components: air pump, tubing, facemask**



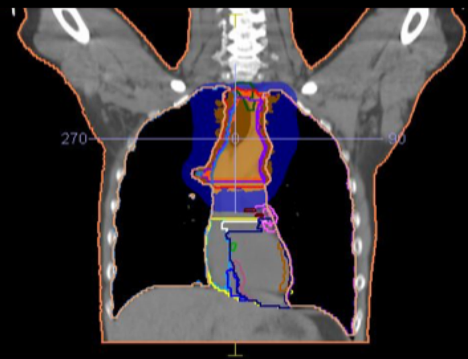
Respiratory gating @ UniTo: C-PAP & Radiotherapy

- Prospective observational study
- HL and PMBCL with mediastinal involvement
- Airway pressure: 18 cmH_2O
- Dosimetric comparison of 2 different VMAT approaches: FREE-Breathing vs C-PAP

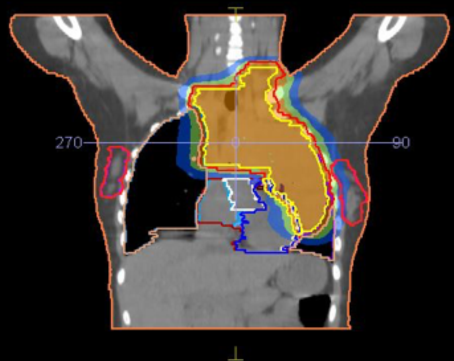


Free-Breathing | **With C-PAP**

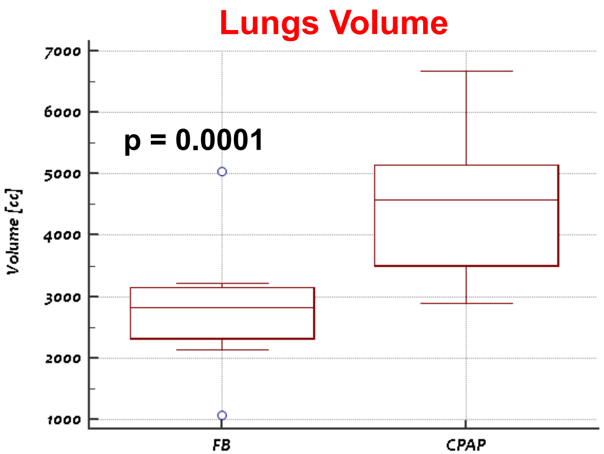
MALE PATIENT

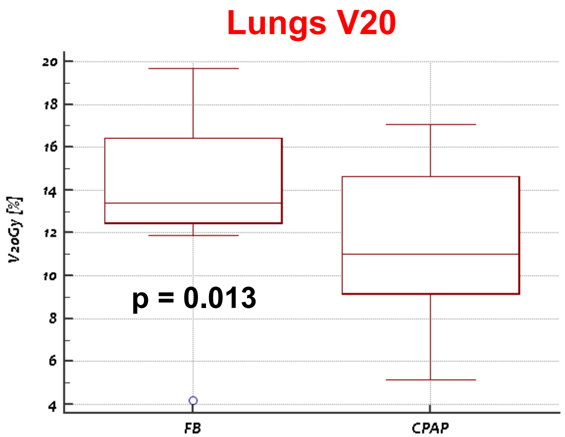


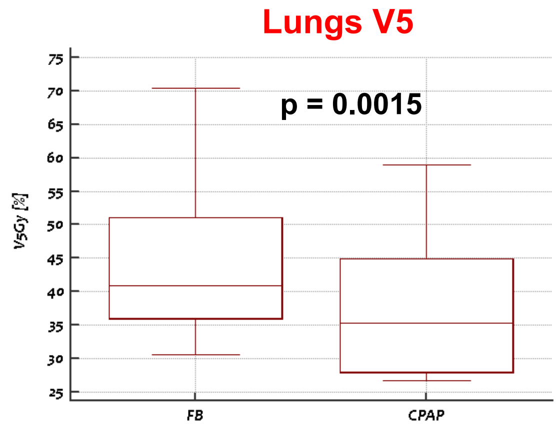
FEMALE PATIENT



DOSIMETRIC COMPARISON (Lungs)







Preliminary results (10 patients) – submitted to ESTRO38, Milan 2019

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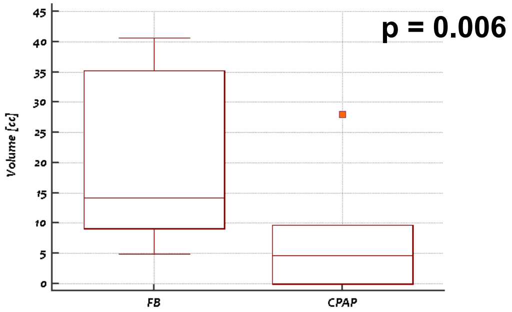
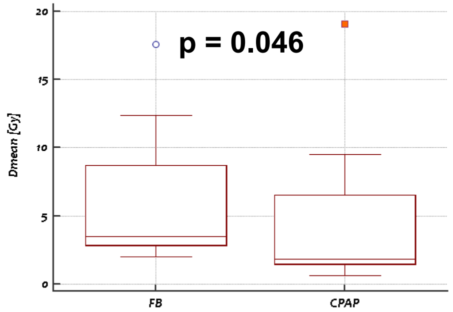
DOSIMETRIC COMPARISON (Heart)

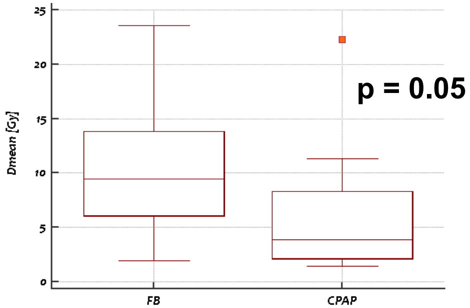
Intersection PTV/Heart (cc)



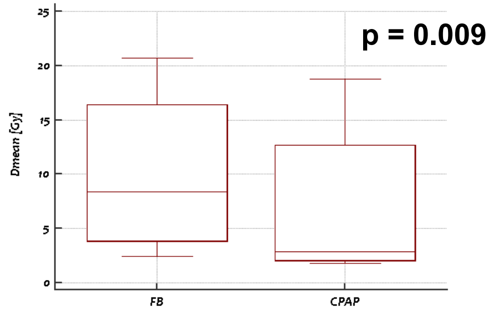
Mean Heart Dose (Gy)



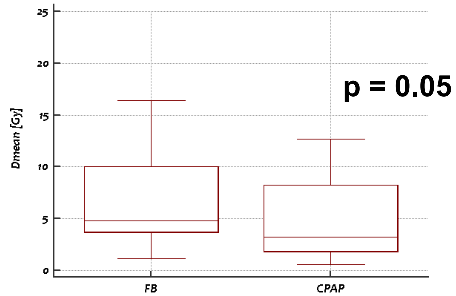
Aortic Valve (mean dose)



Circumflex (mean dose)



Left descending (mean dose)



Preliminary results (10 patients) – submitted to ESTRO38, Milan 2019

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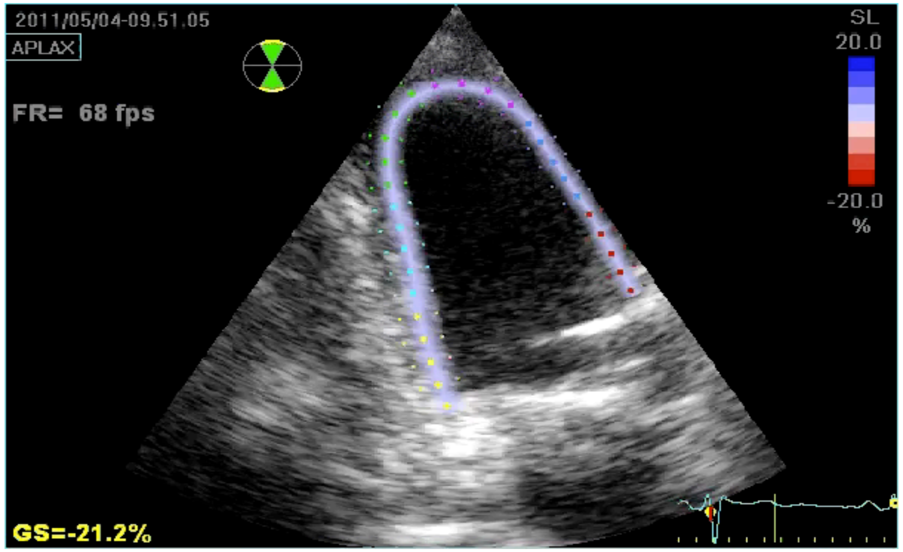
4

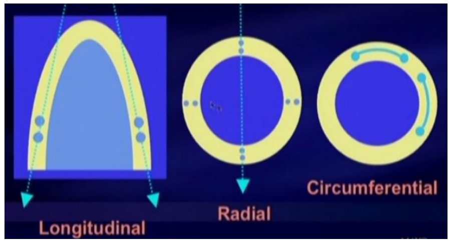
EARLY DIGNOSIS OF SUBCLINICAL "RIHD"

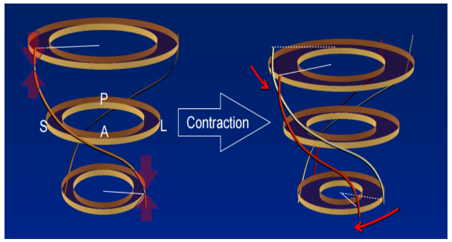
THE ”ONE MILLION DOLLAR” QUESTION

DO WE HAVE ANY TOOL TO DETECT TREATMENT RELATED HEART TOXICITY IN A PRECLINICAL PHASE?

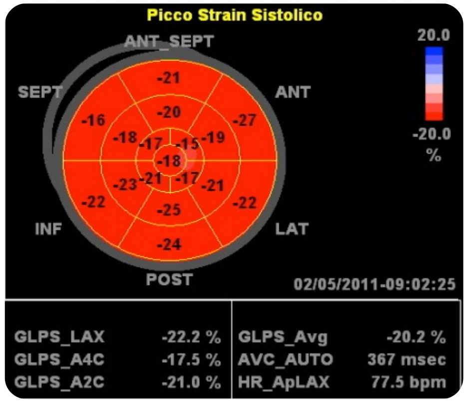
Advanced Ultrasound Imaging
2D Global Longitudinal Strain – “SPECKLE TRACKING”



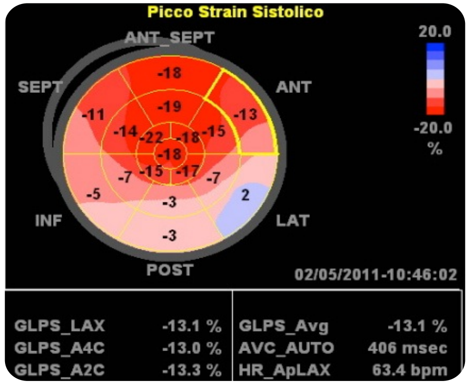




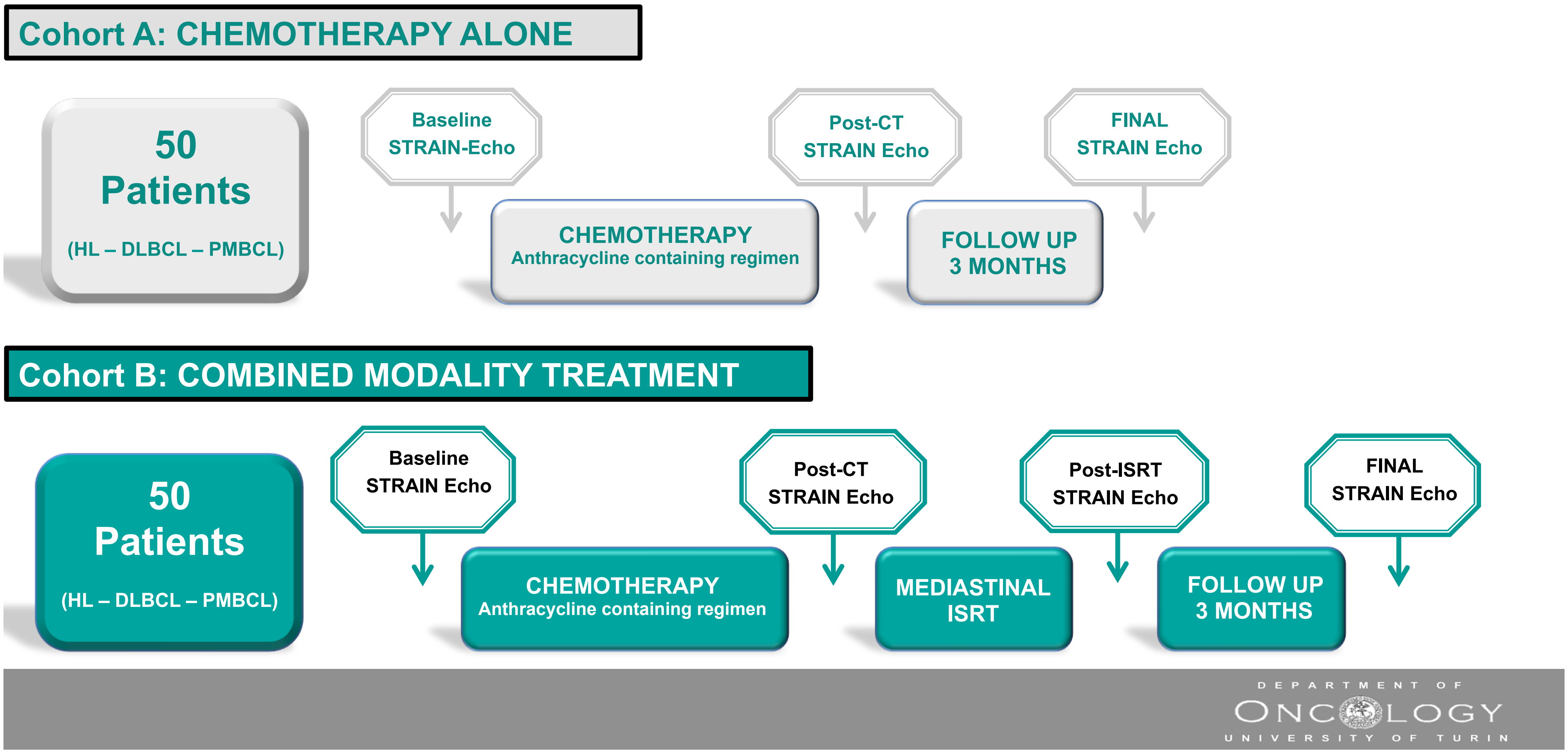
Normal
GLS systolic peak



After STEMI
GLS systolic peak

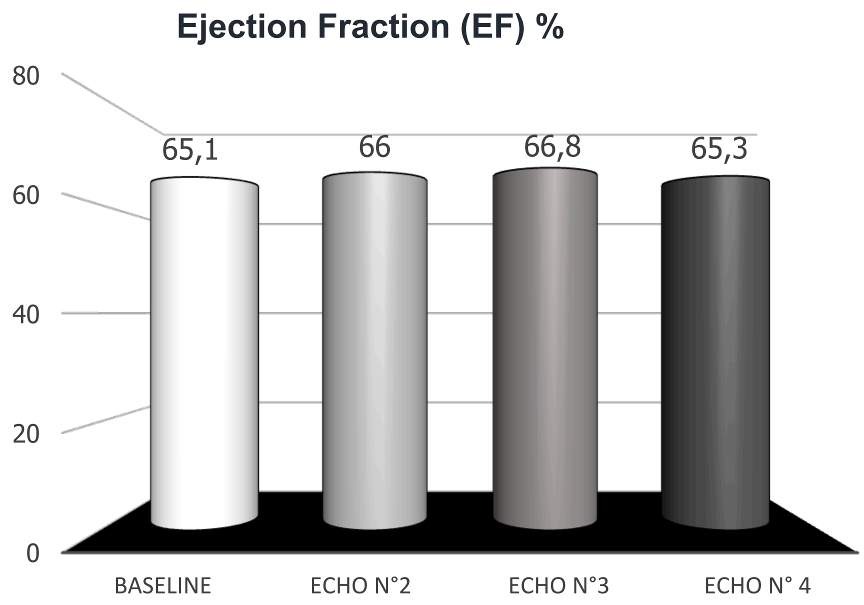


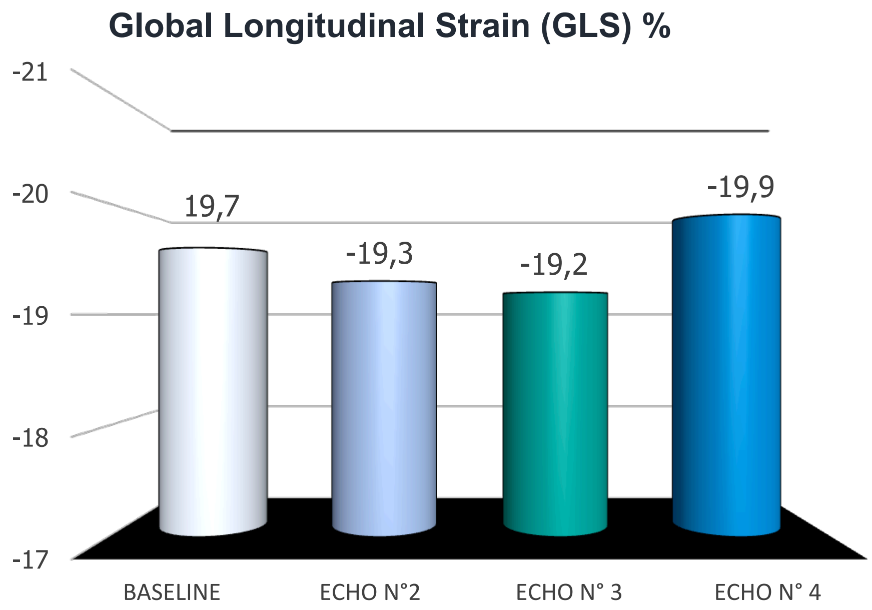
CARDIOCARE Project *University of Torino*



RESULTS (systolic parameters)

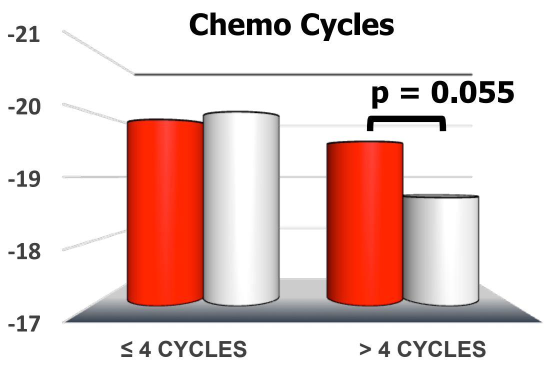
- Interim results on **52** patients
  - **24** in cohort A: Chemo alone
  - **28** in cohort B: Chemo + ISRT

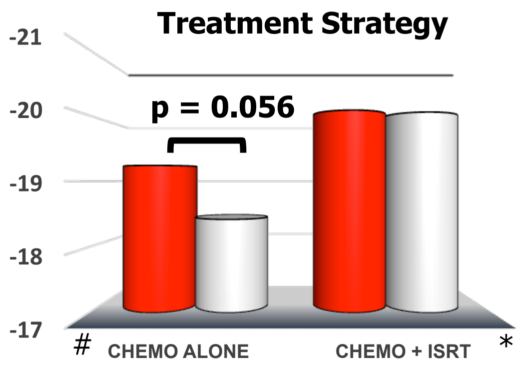




Levis M, et al. Oral communication, ASTRO 2018, San Antonio, USA

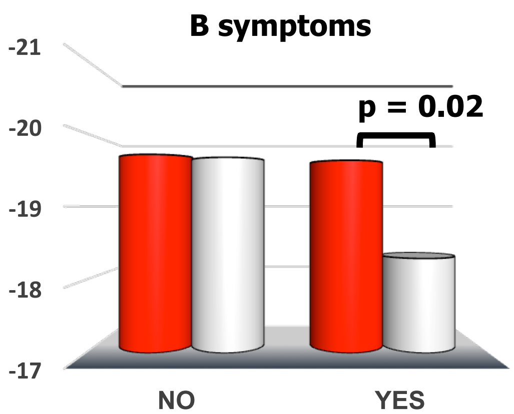
RESULTS
(GLS changes after chemo)
Subgroup analysis

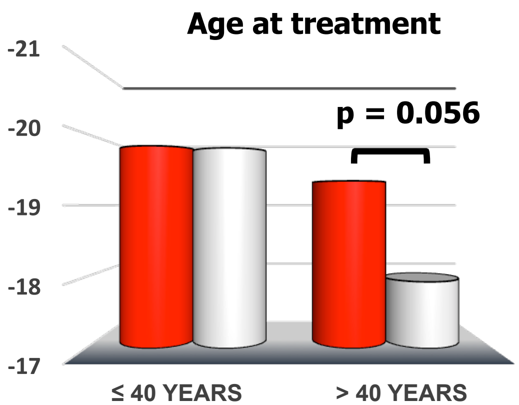




median anthracycline dose: 500 mg

* median anthracycline dose: 400 mg

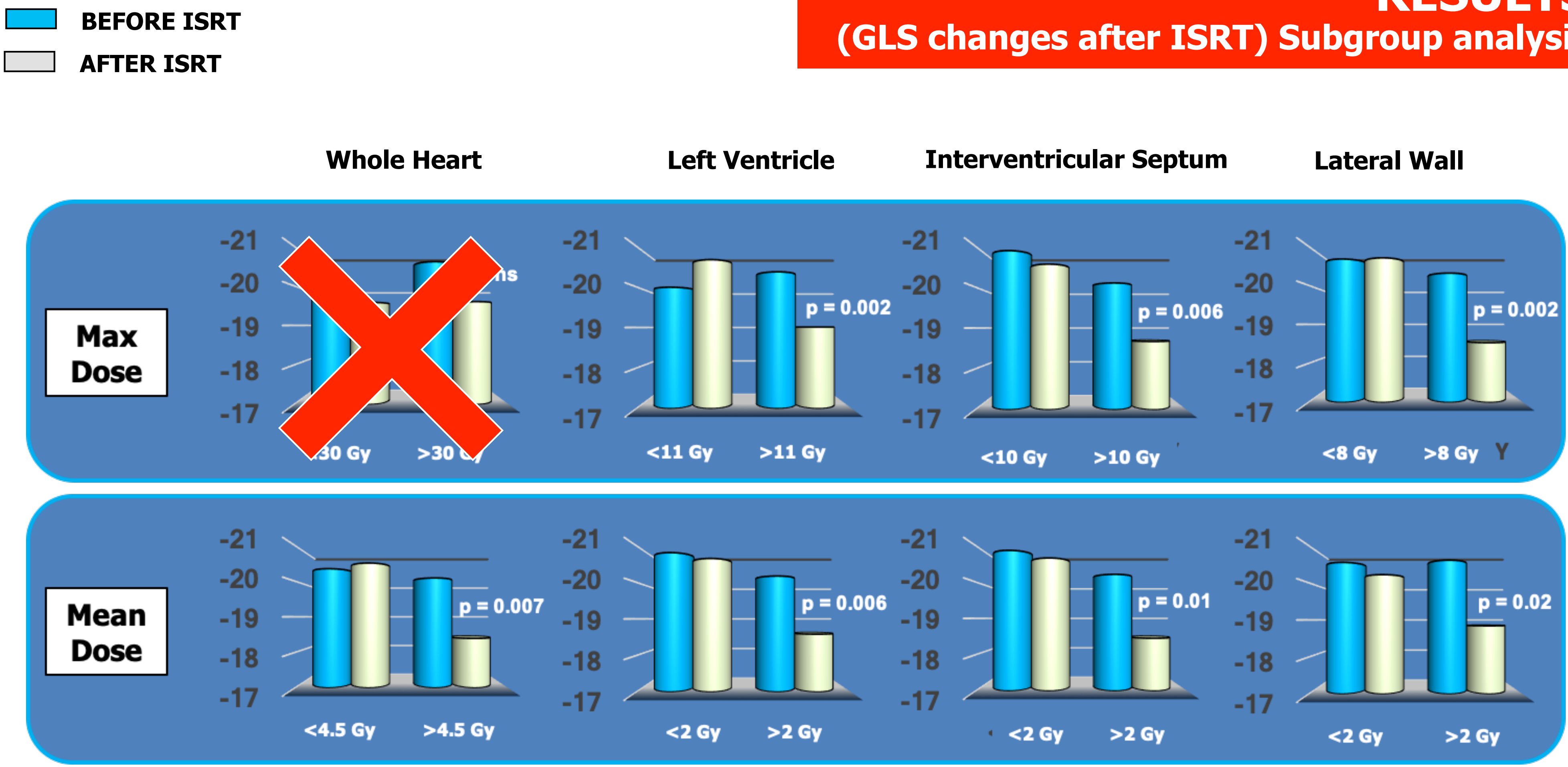




BASELINE

AFTER CHEMO

RESULTS
(GLS changes after ISRT) Subgroup analysis



Levis M, et al. Oral communication, ASTRO 2018, San Antonio, USA

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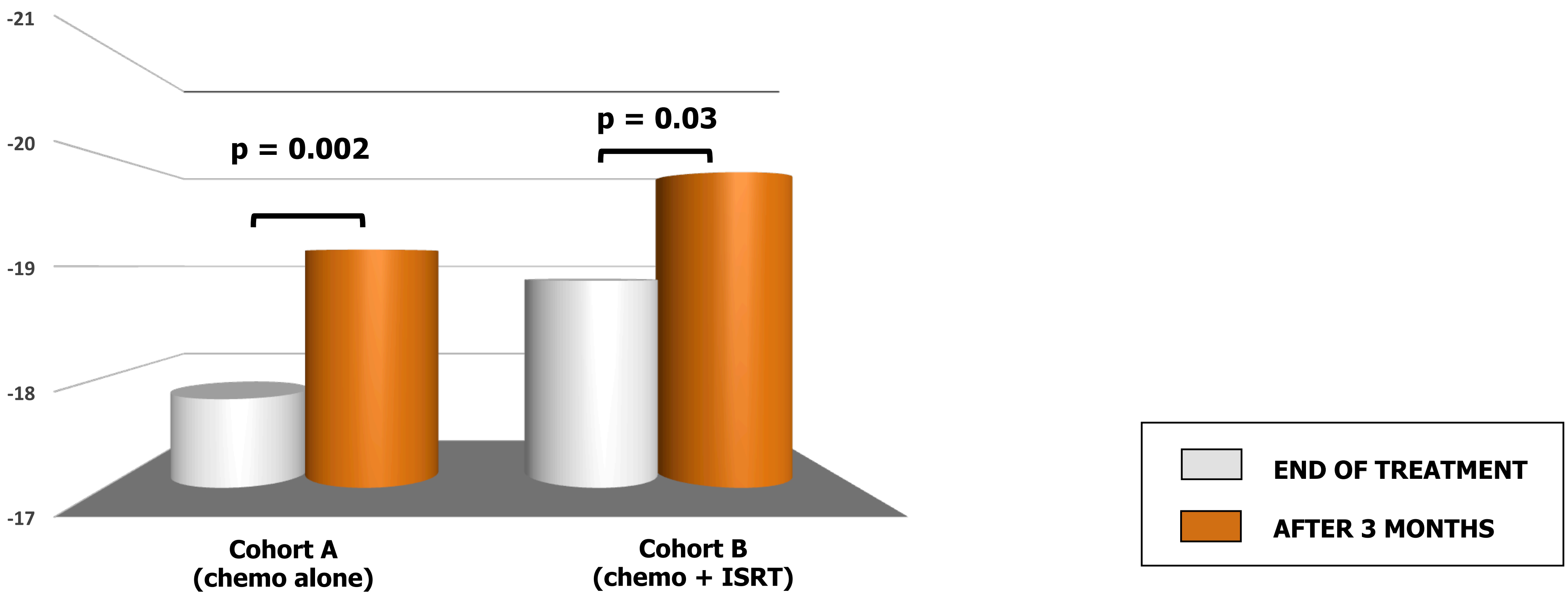
RESULTS
(GLS recovery 3 months after end of treatment)



Levis M, et al. Oral communication, ASTRO 2018, San Antonio, USA

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Dr. D. Caracciolo
Giorgio Priolo

CONCLUSIONS

1) Based on the published data, THORACIC RADIATION THERAPY REPRESENTS A RISK FACTOR FOR LONG TERM CARDIAC EVENTS, and all the clinicians involved in the management of these patients should be aware of this information

2) "Modern" radiotherapy is PROBABLY LESS TOXIC compared to "older" approaches, but we must wait many years to confirm this assumption

3) Actual and future directions include a strong effort to contour the organs at risk (particularly, the cardiac substructures) of patients receiving mediastinal irradiation in order to obtain SPECIFIC AND CLINICALLY MEANINGFUL DOSE CONSTRAINTS, based on a correlation with clinically relevant cardiac events.

4) Need for new tools to detect CHEMO/RT INDUCED heart toxicity in a PRECLINICAL PHASE

Protect Your HEART

You

Only

Have One