Radiotherapy: new technologies and reduction of heart damage

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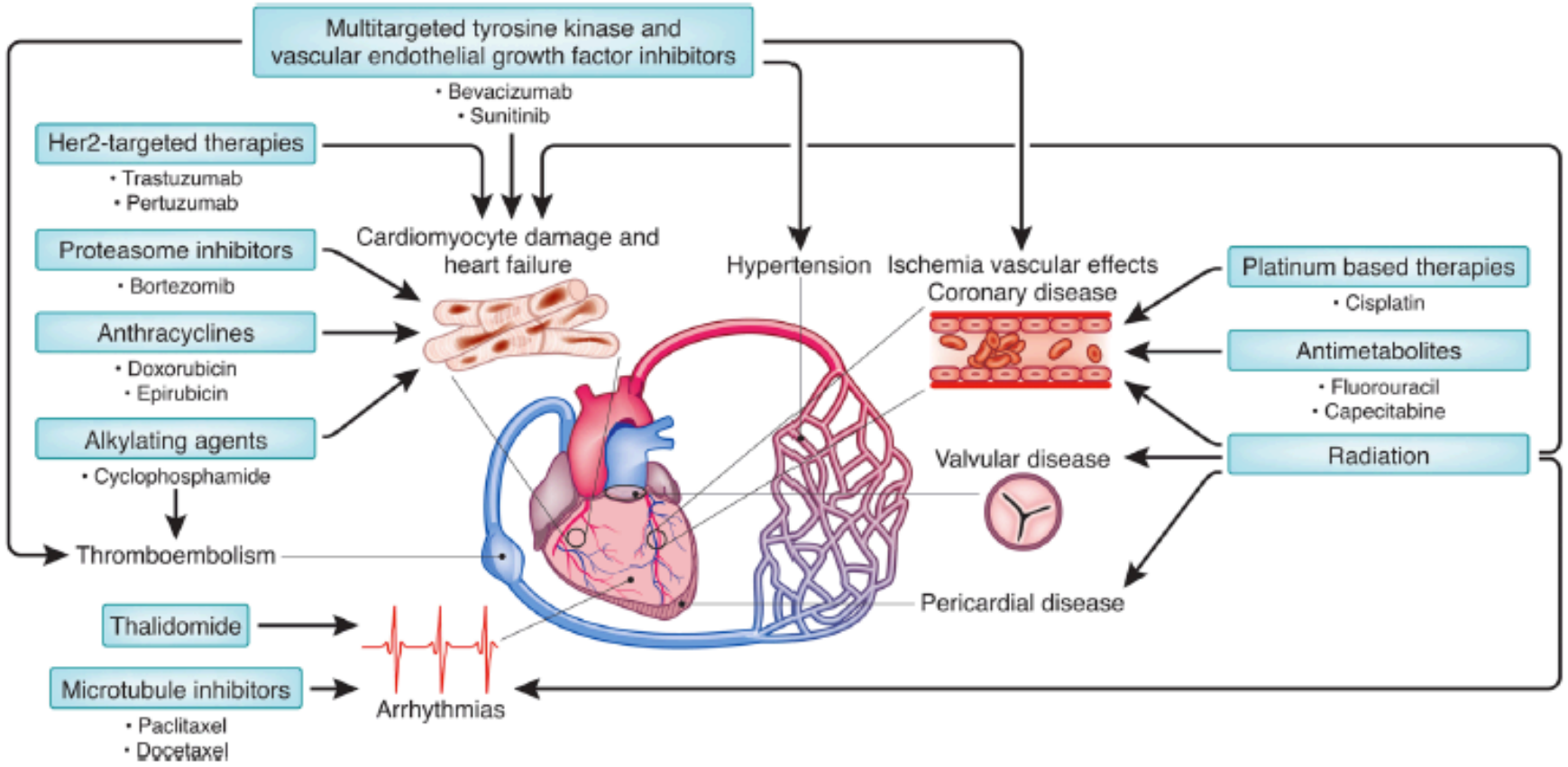
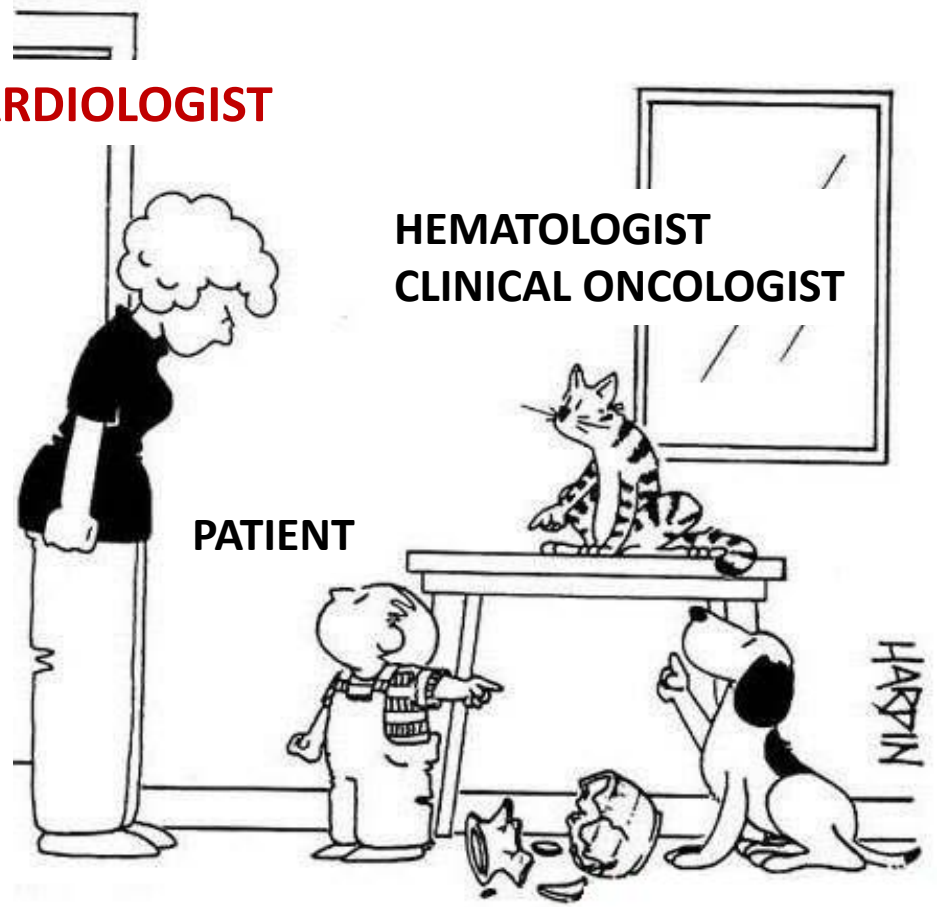
TREATMENT RELATED TOXICITY IN LONG TERM SURVIVORS
1970 – 1980 knowledge…

RADIATION INDUCED HEART TOXICITY: A COMPLEX AND RELATIVELY RECENT HISTORY



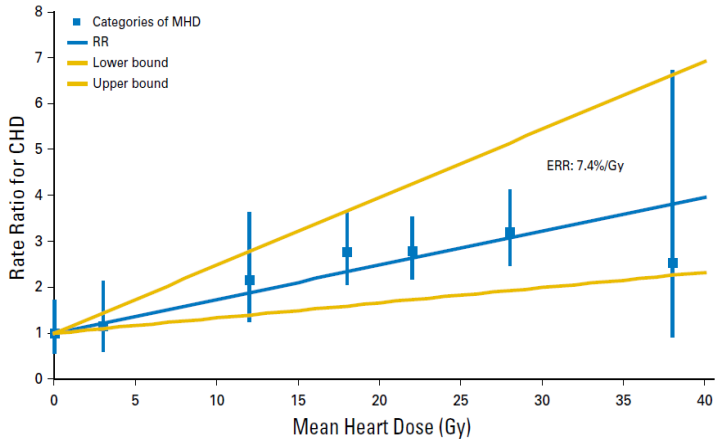
Treatment Related Cardiac Events In Long Term Cancer Survivors:

WHO IS THE GUILTY ONE?



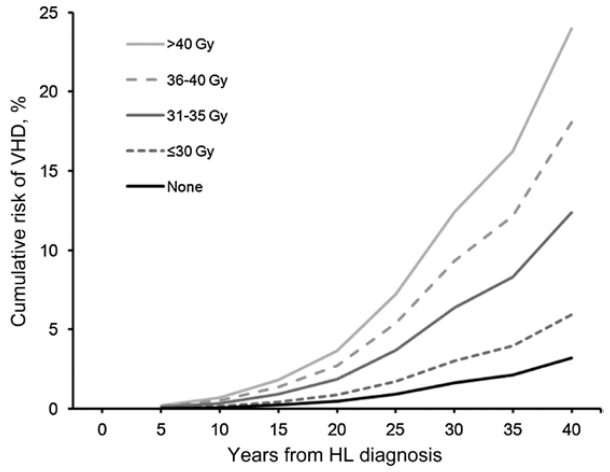
Radiation Induced Heart Toxicity
Linear correlation between heart dose and cardiac events

MHD
and development of CAD



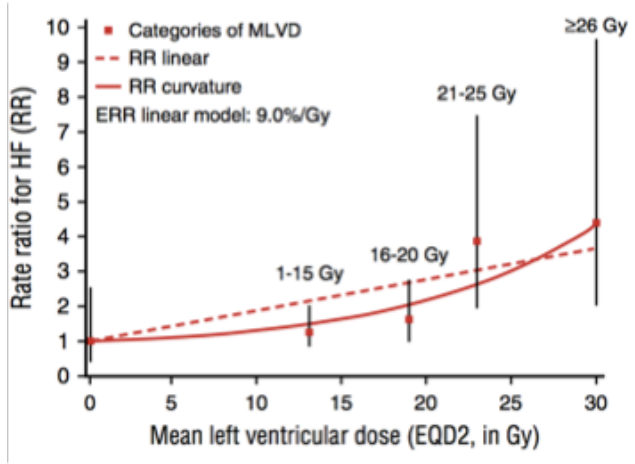
van Nimwegen et al. JCO 2016

Valvular dose
and development of VHD



Cutter et al. JNCI 2015

MLVD
and development of CHF

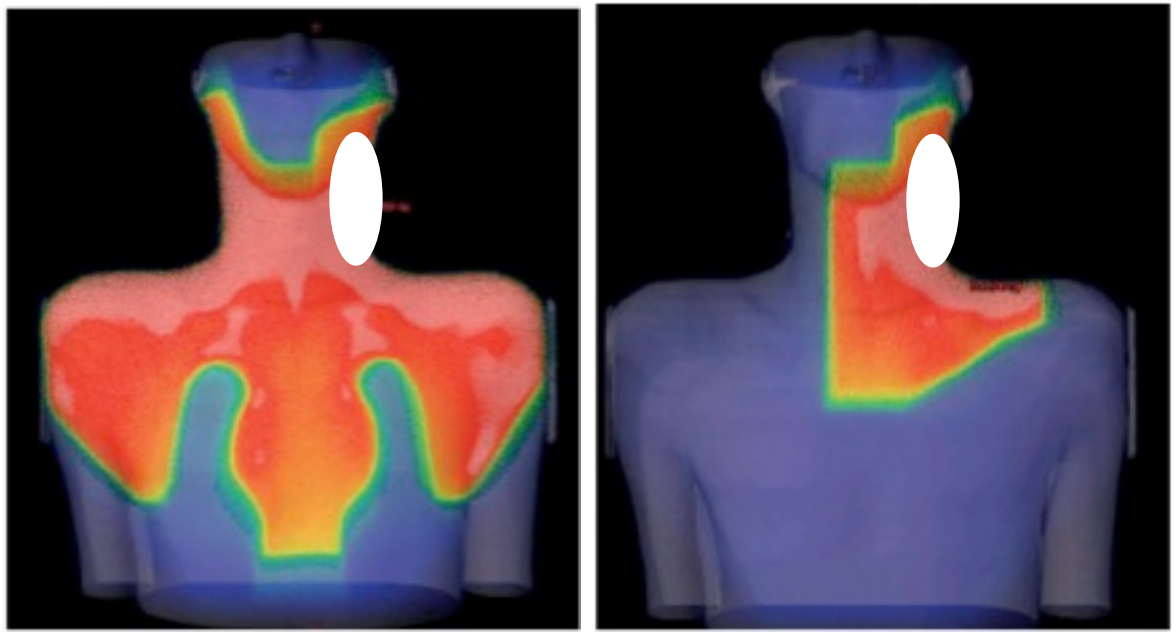


van Nimwegen et al. Blood 2017

But…RT has got many improvements in the recent years

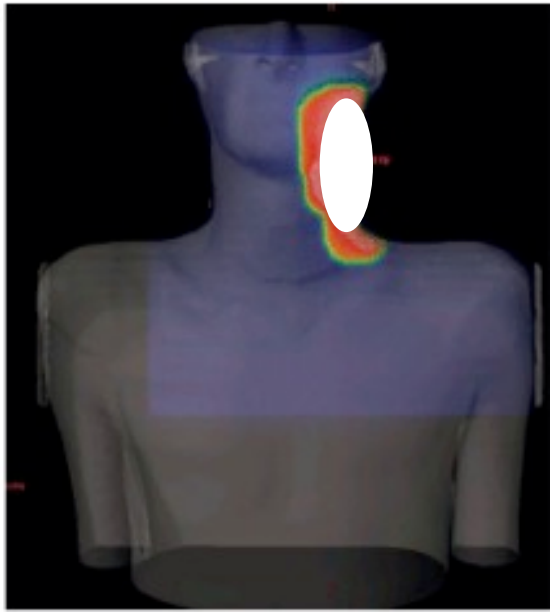
Mantle field

Involved field



Volume treated on the basis of anatomical borders

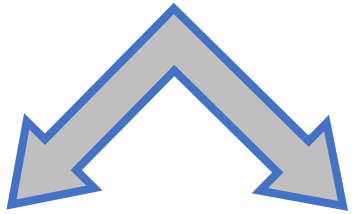
Involved site
Involved node



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

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)

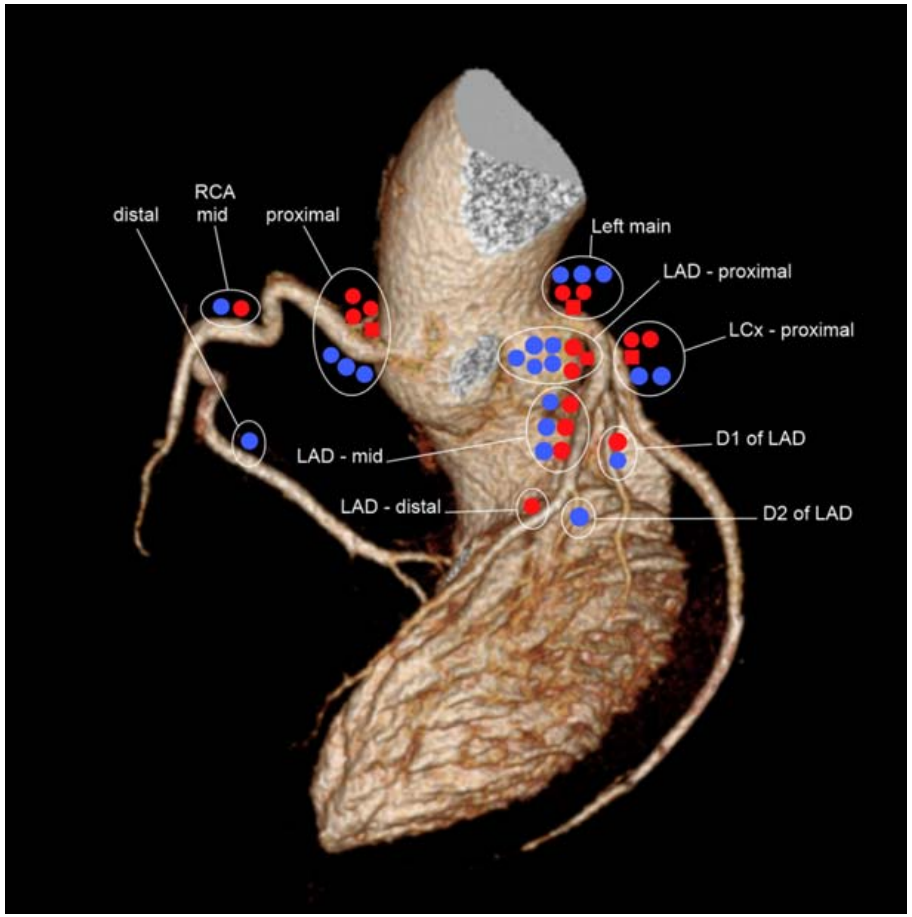
- ❑ Diagnostic tools
  1. Biomarkers *(Troponine, NTproBNP, miRNA)*
  2. Echocardiography
  3. Cardiac MRI
  4. Coronary angiography CT scan

1

PROSPECTIVE AND DETAILED CONTOURING OF THE HEART STRUCTURES

Coronary Artery Disease Detected by Coronary Computed Tomography Angiography in Adult Survivors of Childhood Hodgkin Lymphoma

Location of Plaque	No. (%)
Left main artery	6 (15)
Left anterior descending artery	
Proximal	8 (21)
Middle	6 (15)
Distal	1 (3)
Diagonals	2 (5)
Left circumflex artery	
Proximal	5 (13)
Distal	0 (0)
Right coronary artery	
Proximal	7 (18)
Middle	2 (5)
Distal	2 (5)



✧ ***31 asymptomatic patients screened for coronary disease >15 years past the treatment for HL***

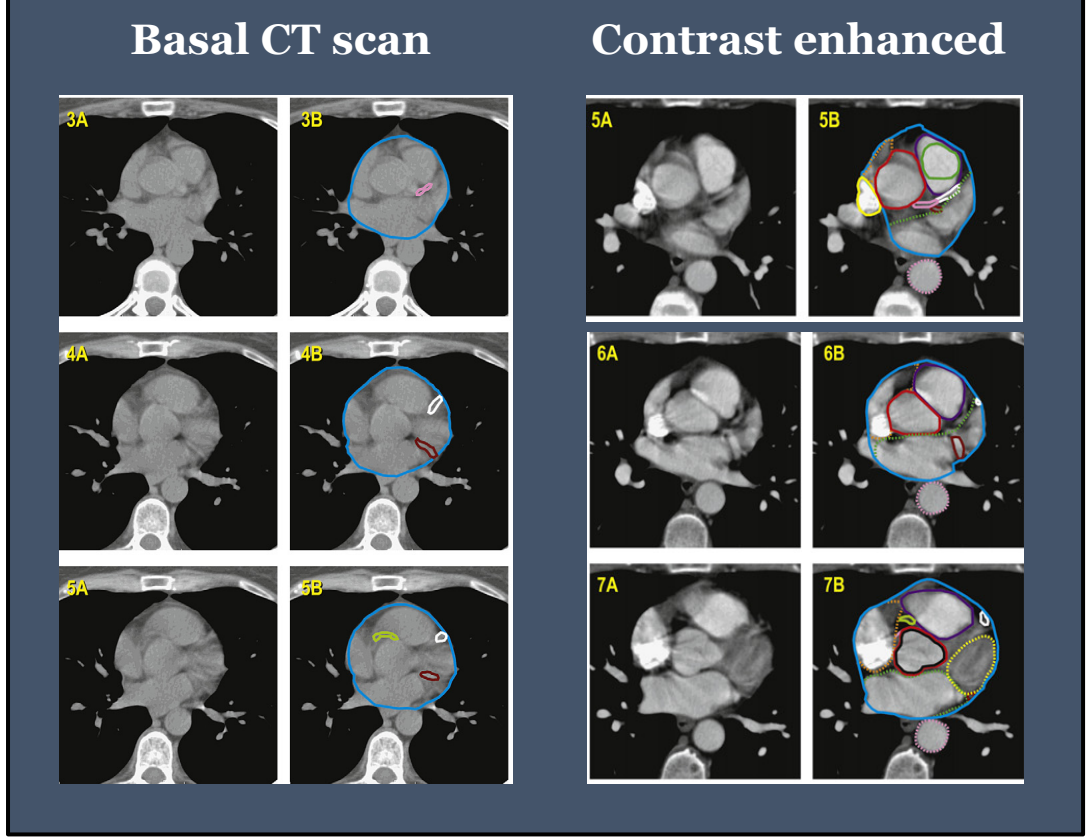
✧ ***CAD prevalence: 39% (normal population: 8.5-11%***

Mulrooney at al, Cancer; 2014

CONTOURING OF THE HEART STRUCTURES

CLINICAL INVESTIGATION **Breast**

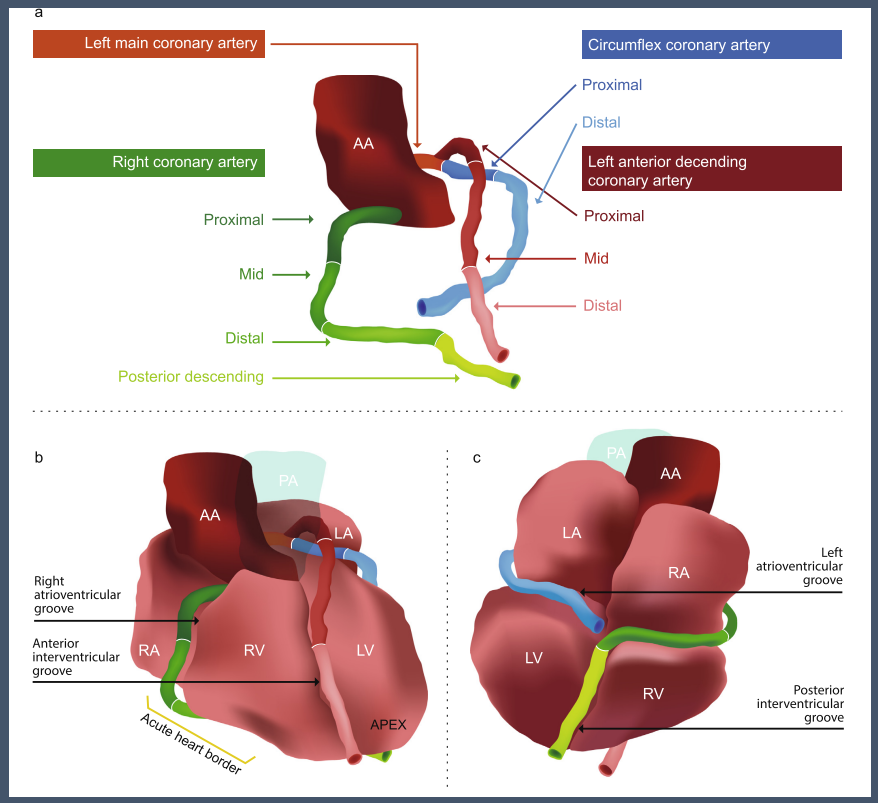
DEVELOPMENT AND VALIDATION OF A HEART ATLAS TO STUDY CARDIAC EXPOSURE TO RADIATION FOLLOWING TREATMENT FOR BREAST CANCER



Feng M et al. IJROBP 2011

A cardiac contouring atlas for radiotherapy

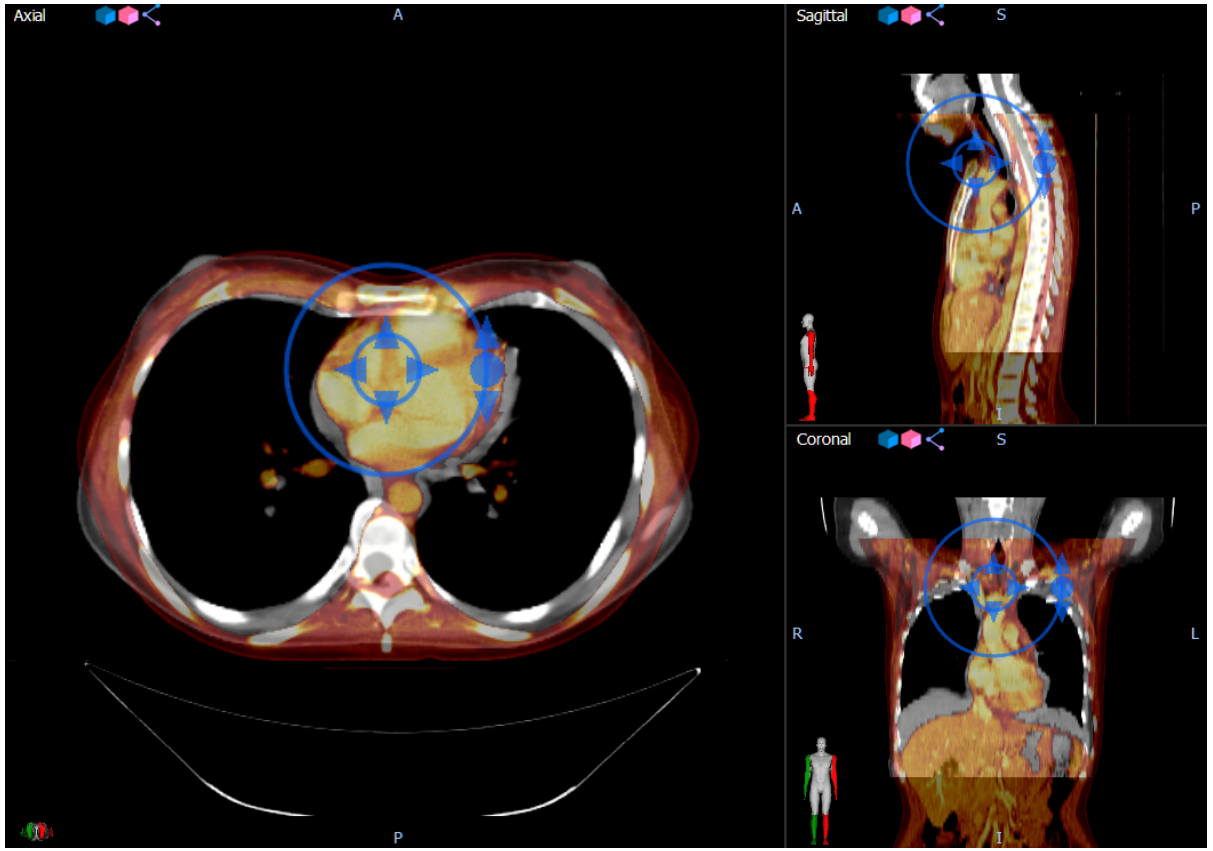
Frances Duane [a,b,*], Marianne C. Aznar [a], Freddie Bartlett [c], David J. Cutter [a], Sarah C. Darby [a], Reshma Jagsi [d], Ebbe L. Lorenzen [e], Orla McArdle [f], Paul McGale [a], Saul Myerson [g], Kazem Rahimi [h], Sindu Vivekanandan [i], Samantha Warren [j], Carolyn W. Taylor [a]



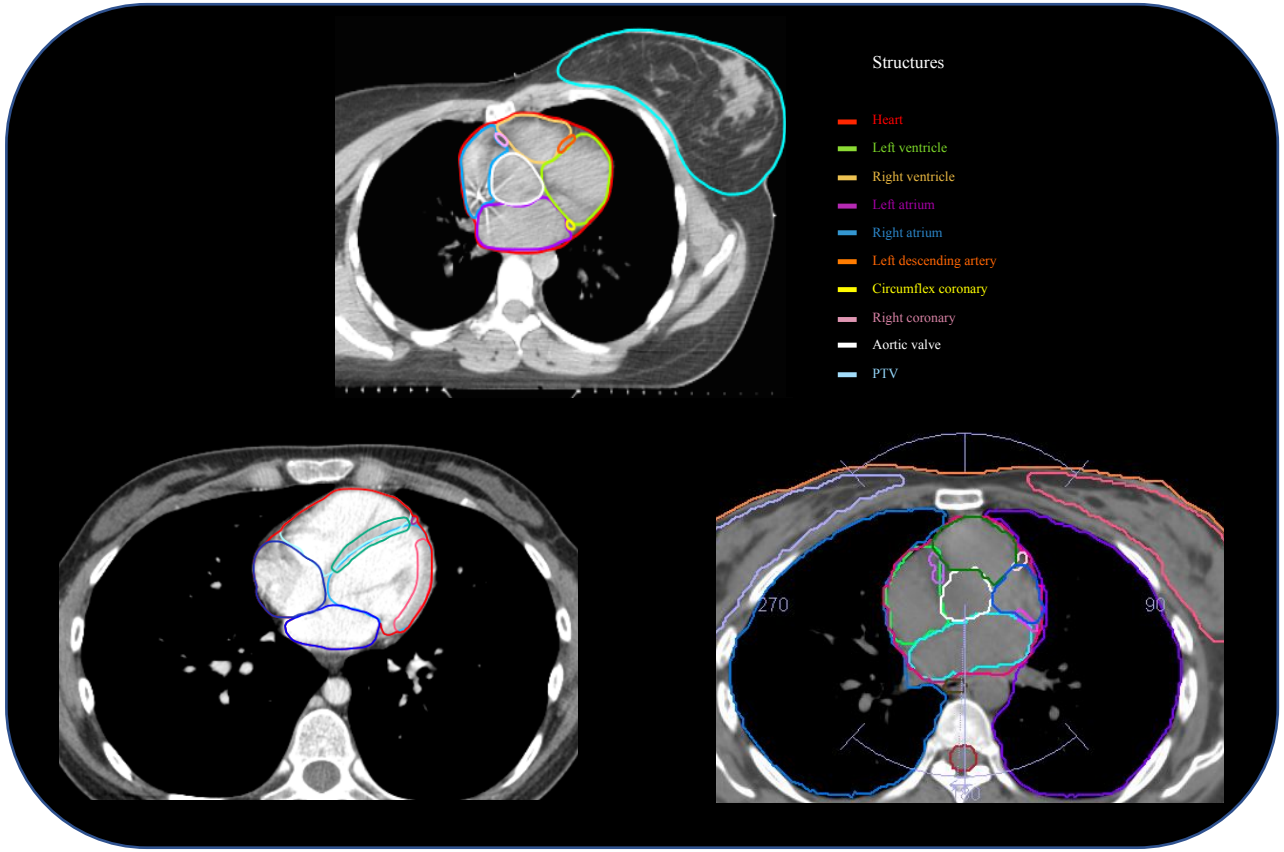
Duane F. et al. Radiother Oncol 2018

TREATMENT PLANNING

1 - Image fusion

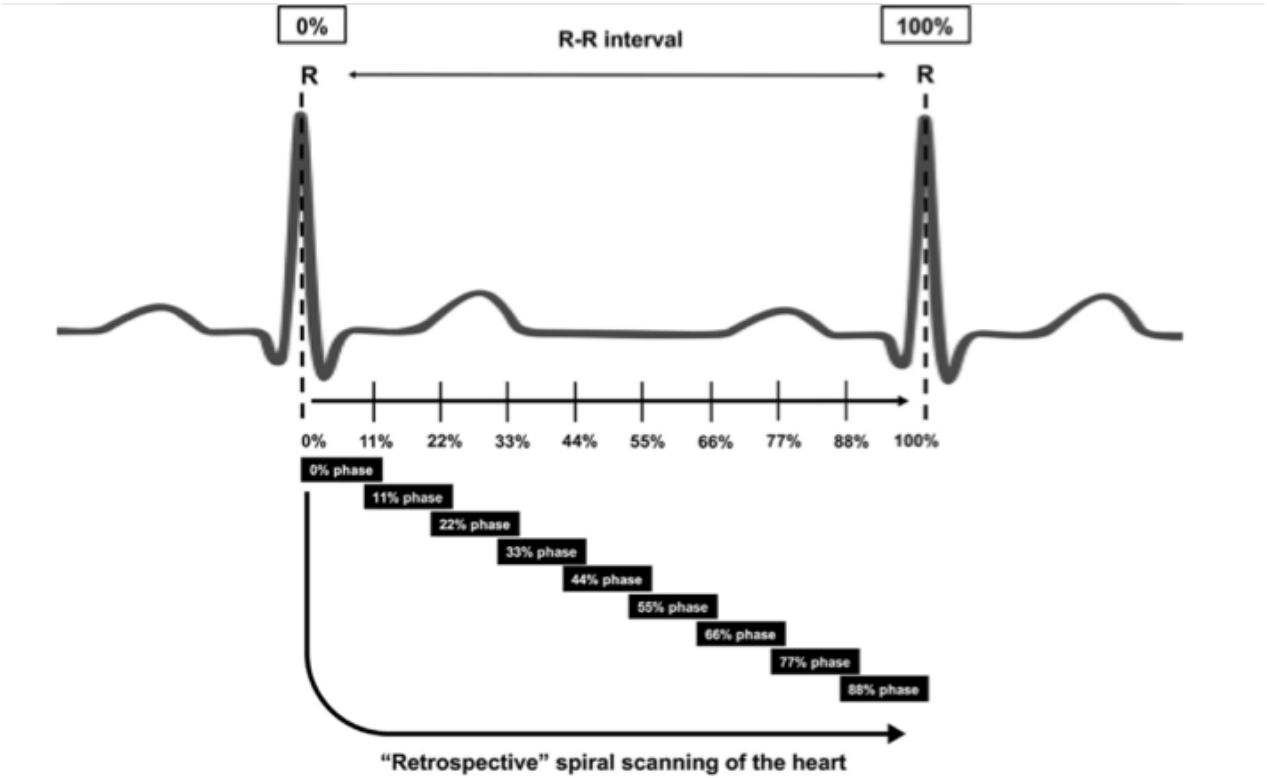


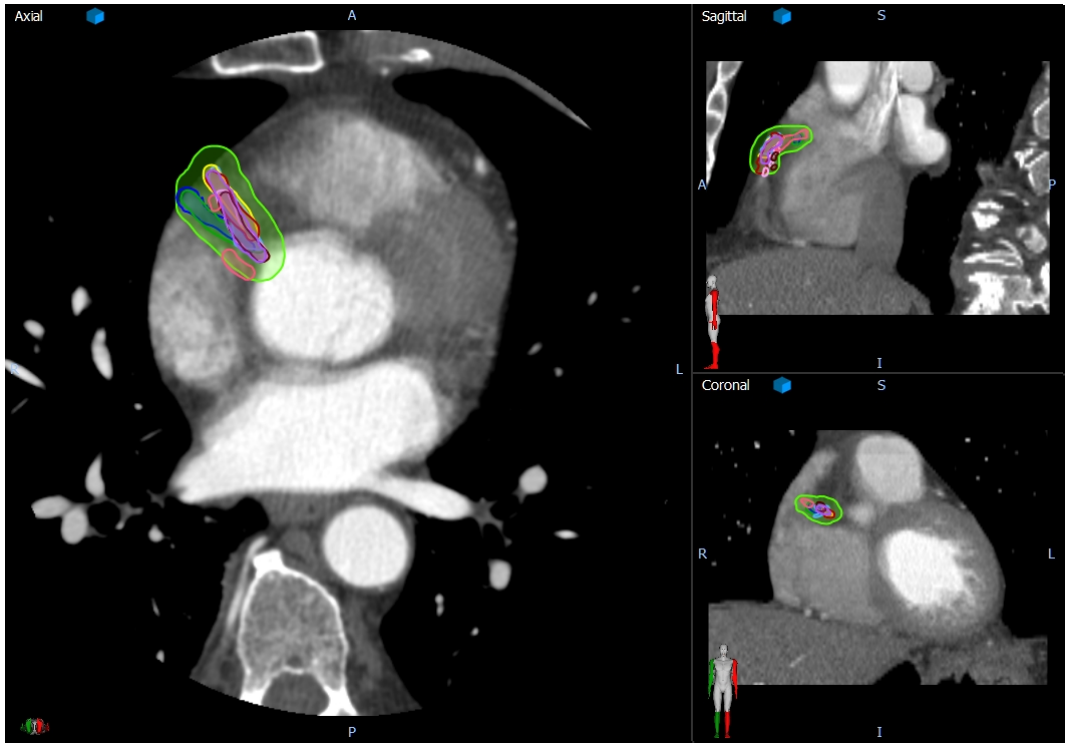
2 – Accurate contouring of cardiac structures

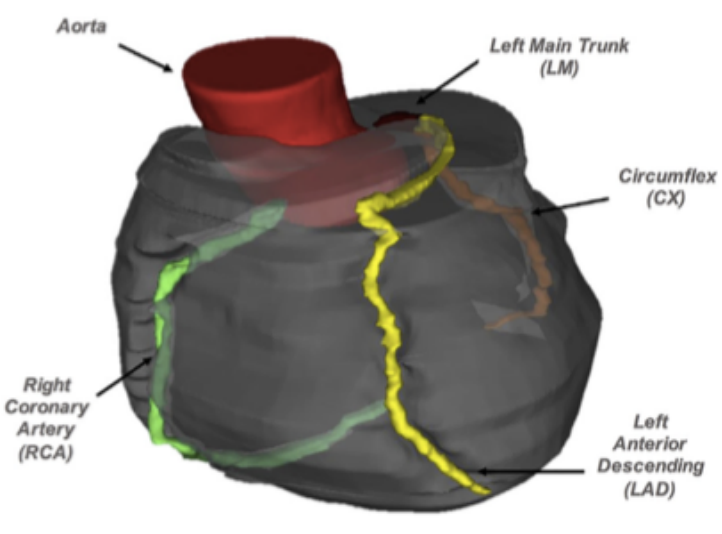


Plan optimization for mediastinal radiotherapy: Estimation of coronary arteries motion with ECG-gated cardiac imaging and creation of compensatory expansion margins

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]







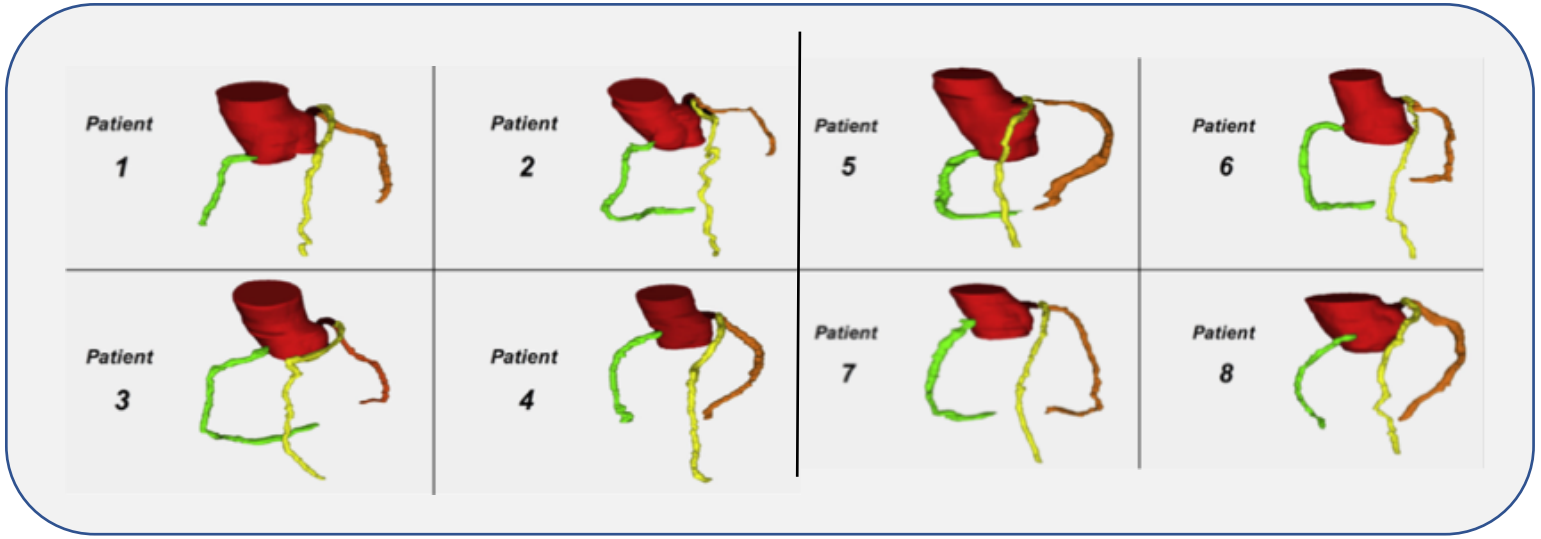


Table 1

Mean coronary arteries displacements evaluated with the McKenzie–van Herk formula [15] for organs at risk ($mPRV = 1.3 * \Sigma + 0.5 * \sigma$), 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

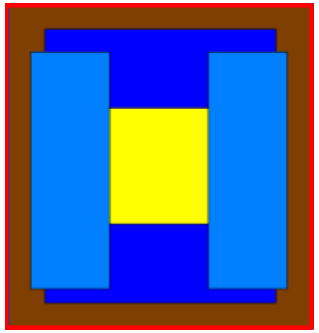
“CHOOSING WISELY”… RT OFFER TAILORED TO THE PATIENTS BY ADOPTING COMPARATIVE PLANNING

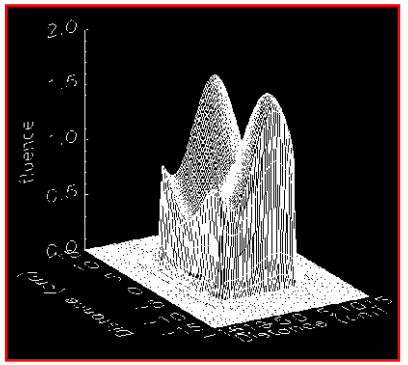
THE CONFORMALITY CONTINUUM

1980s | Late 1990s | 2000s | 2010s

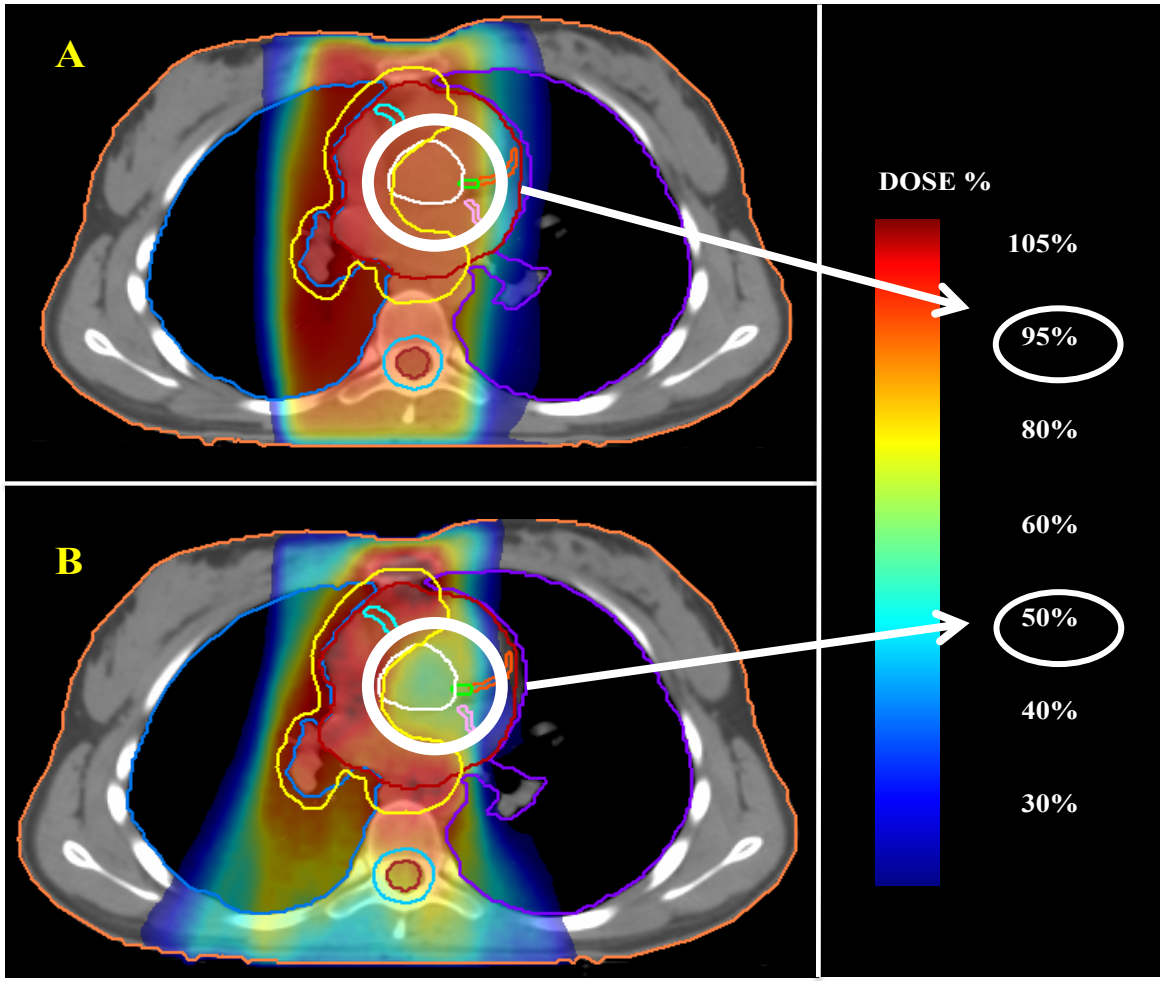
TREND – Improving Precision

2D | 3D-CRT | IMRT/VMAT | IGRT





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

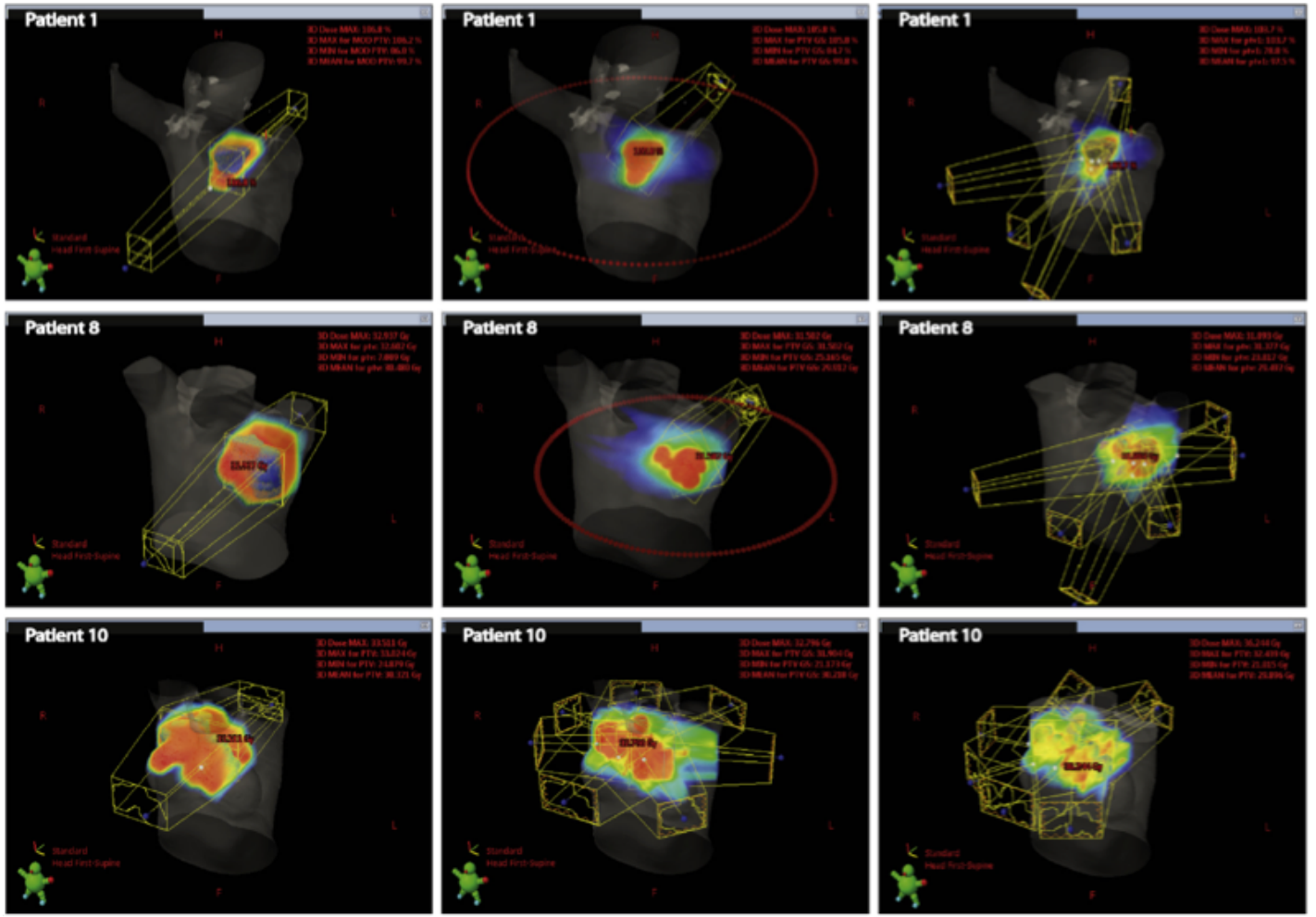


Mean Heart dose similar for 3DCRT and VMAT but…

With VMAT we achieve a better sparing of:

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

CHOOSING WISELY MEANS:
SAME PATIENT, DIFFERENT SOLUTIONS…!



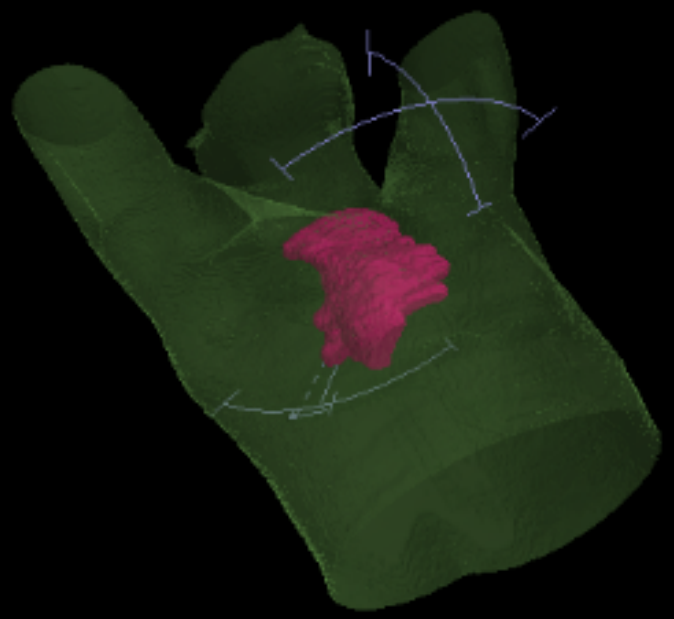
Maraldo MV. et al. IJROBP 2014

RT SOLUTION TAILORED TO PATIENTS' NEEDS

A Butterfly VMAT

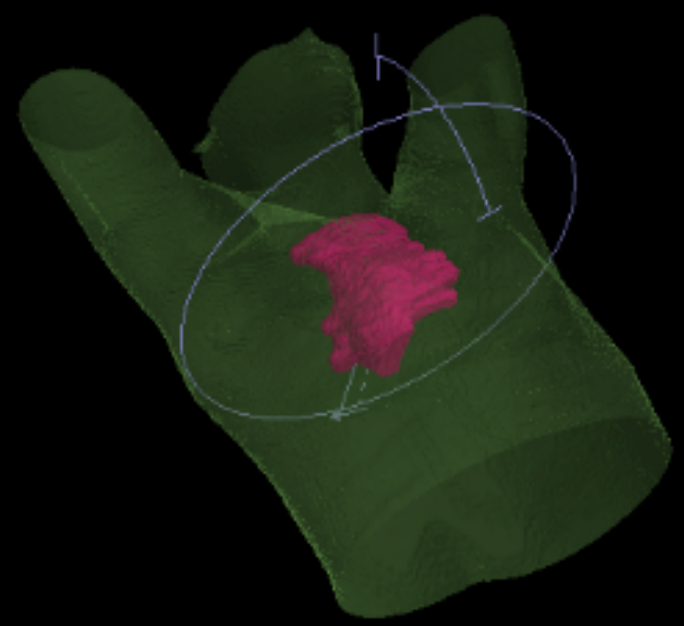
2 coplanar arcs of 60°
- ❑ 1 anterior
- ❑ 1posterior

1 no-coplanar arc of 60°



B Full Arc Butterfly VMAT

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



Levis M, et al. Oral communication, ESTRO 2018, Barcelona, Spain

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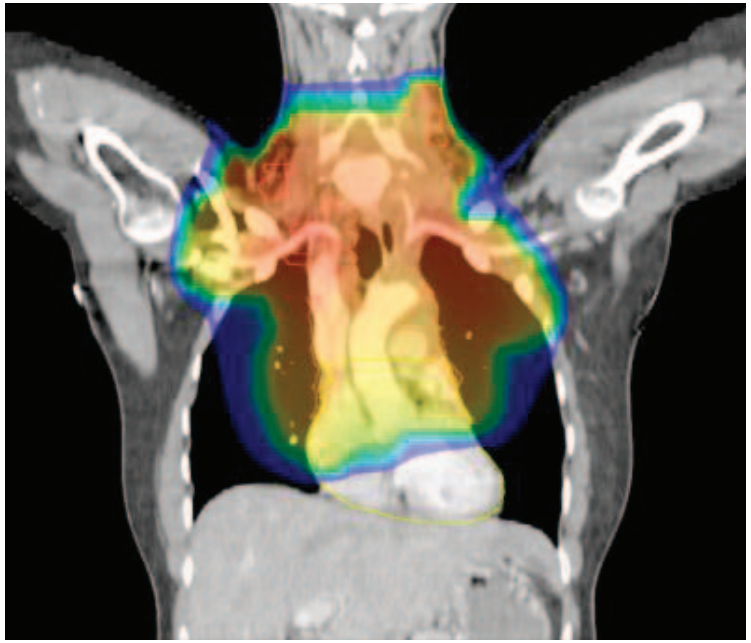
3

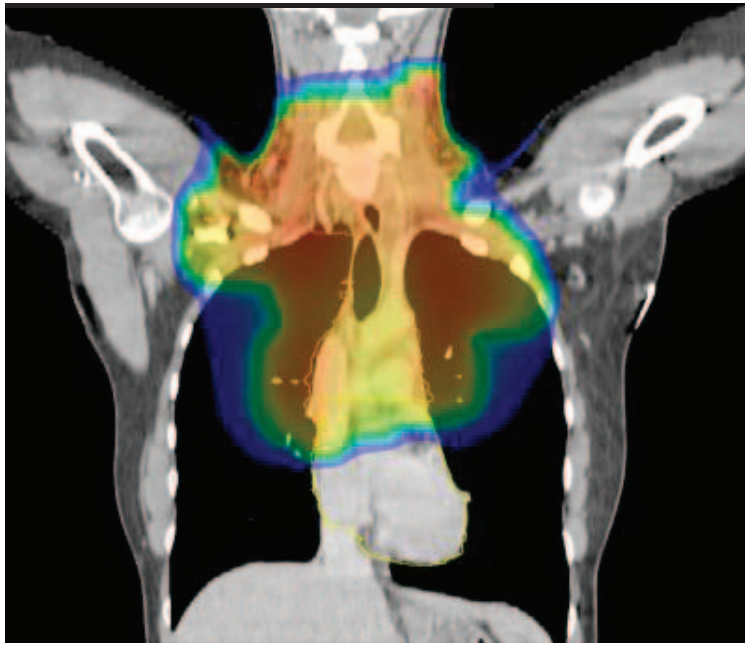
RESPIRATORY GATING (DIBH) INTEGRATED TO MODERN TECHNIQUES

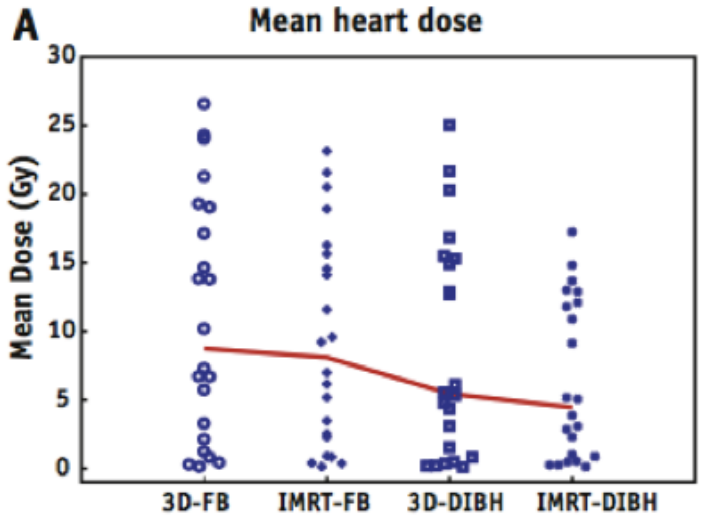
Minimizing Late Effects for Patients With Mediastinal Hodgkin Lymphoma: Deep Inspiration Breath-Hold, IMRT, or Both?

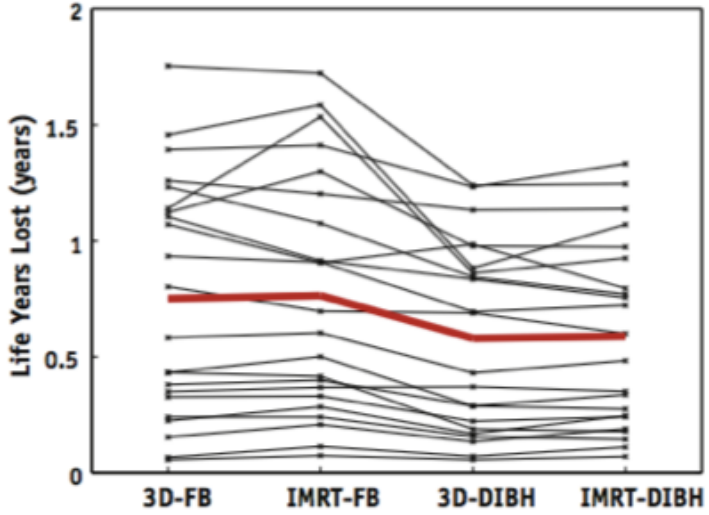
FREE BREATHING

DIBH









Aznar MC et al. IJROBP 2015

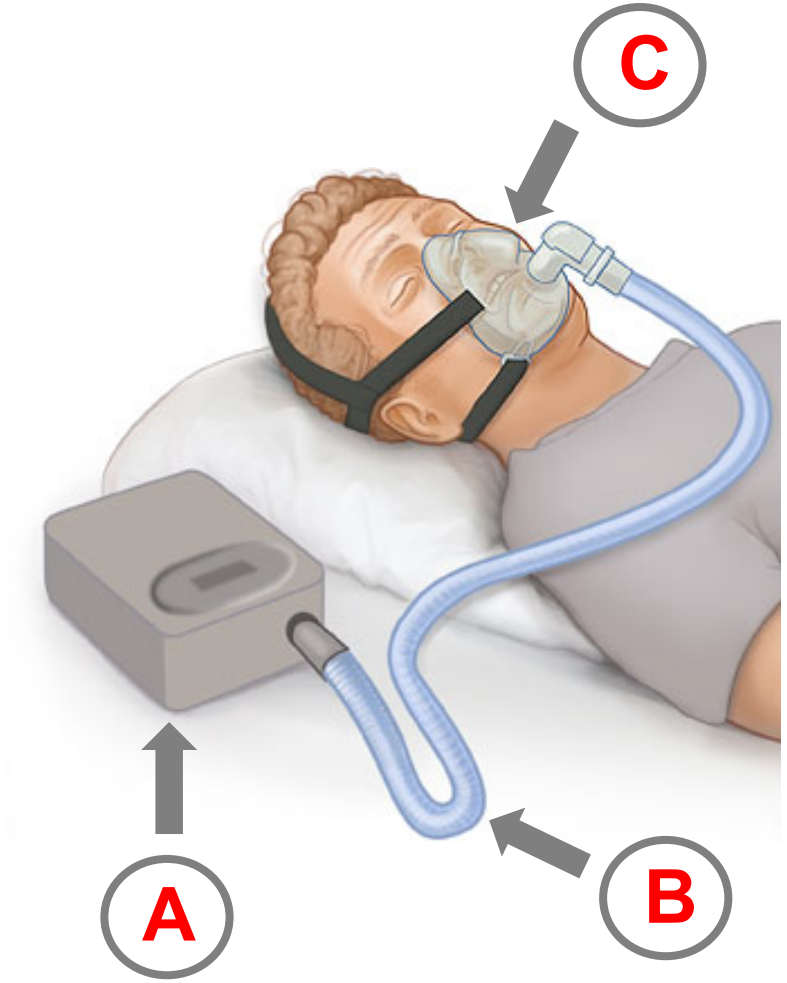
Continuous Positive Airway Pressure (C-PAP):

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.

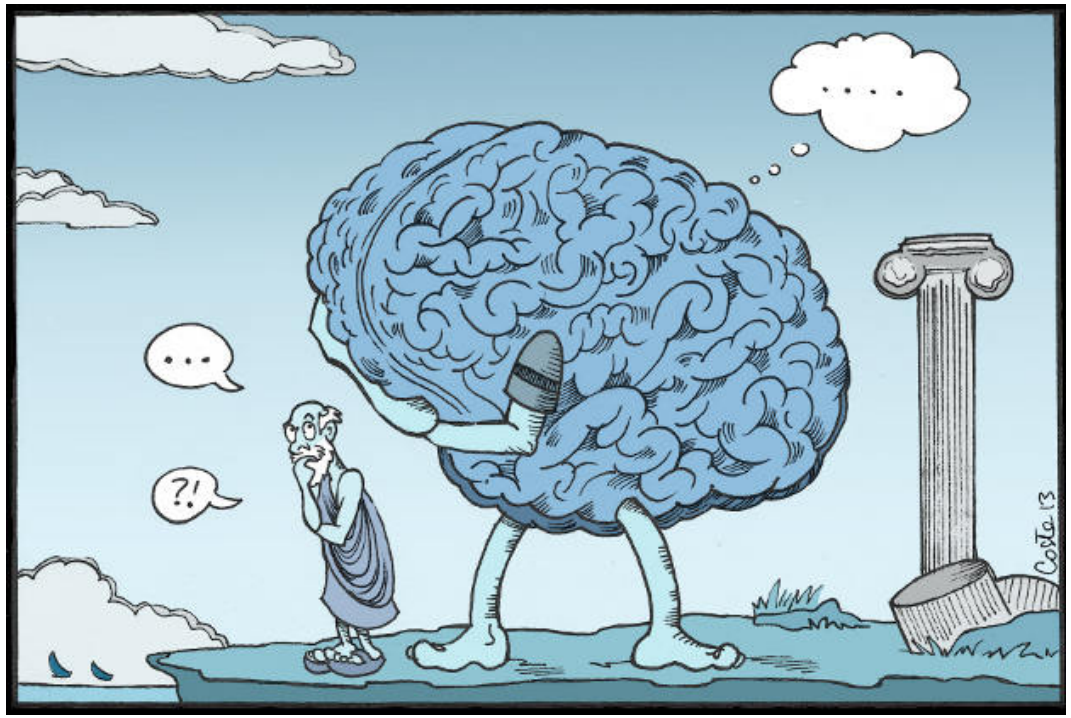
- **Components: air pump, tubing, facemask**



Continuous Positive Airway Pressure (C-PAP):

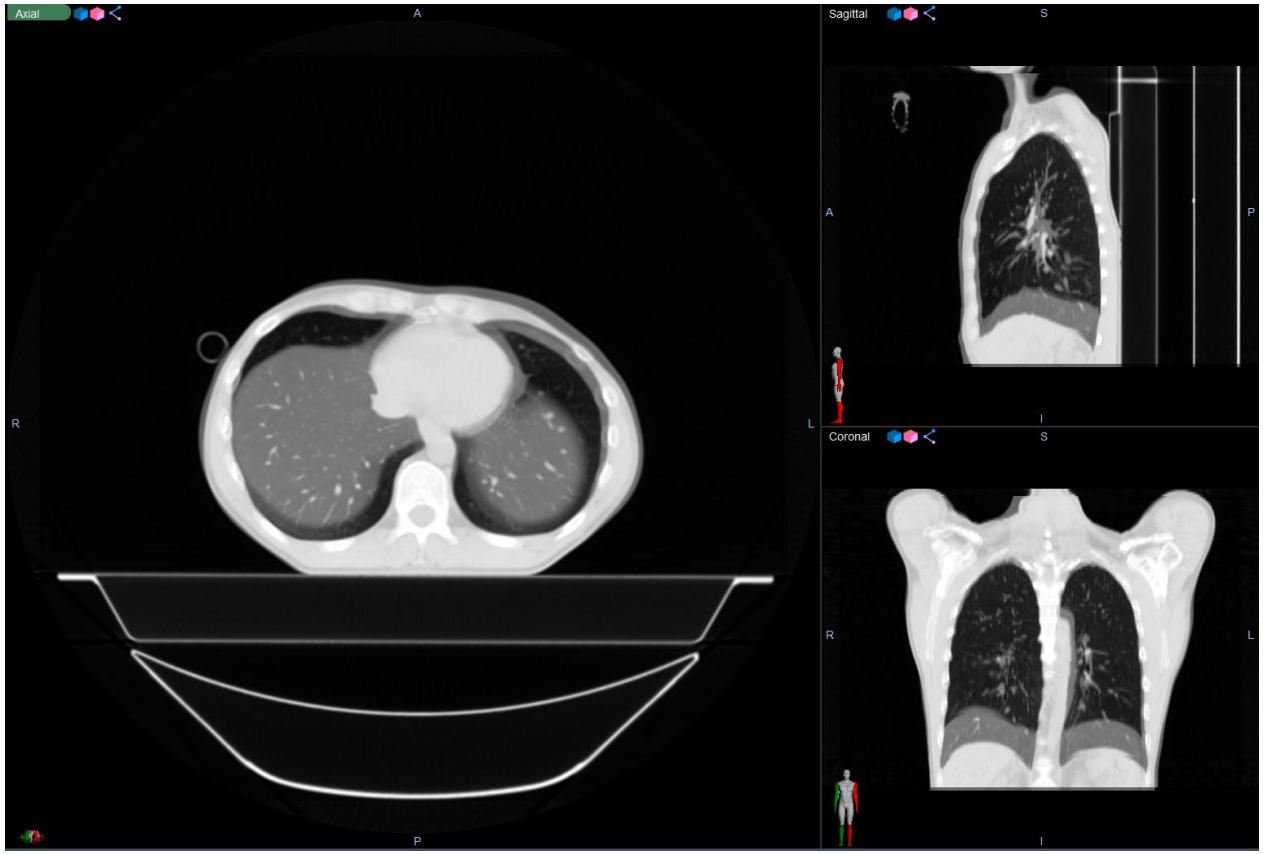
A valuable alternative way for "respiratory gating"?

Hypothesis: The use of CPAP would create favorable radiation treatment geometry in lymphoma patients by expanding (lungs) and displacing (heart) uninvolved organs at risk away from the tumor and out of the beam path.



Respiratory gating @ UniTo: C-PAP & Radiotherapy

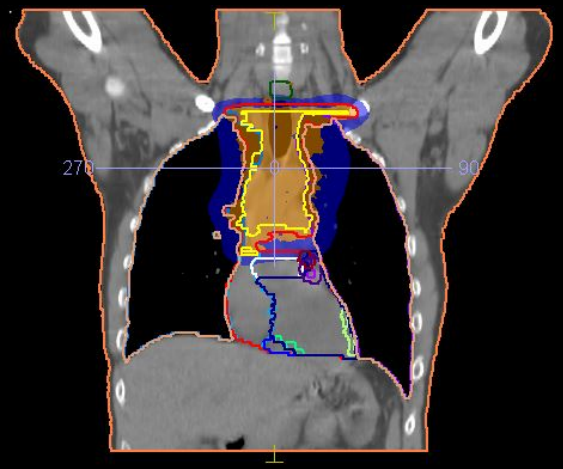
- ❑ Prospective observational study
- ❑ HL and PMBCL with mediastinal involvement
- ❑ Airway pressure: 18 cmH_2O
- ❑ Dosimetric comparison of 2 different VMAT approaches: FREE-Breathing vs C-PAP

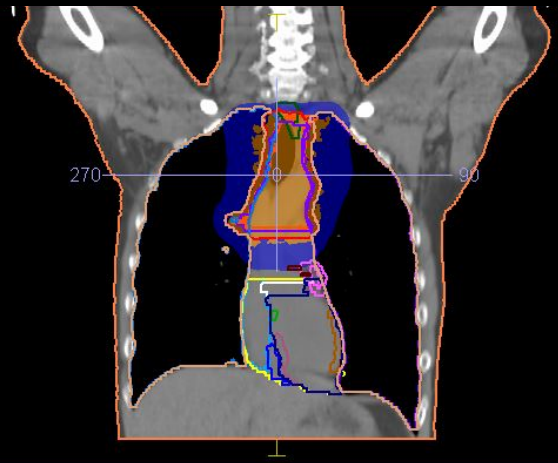


Free-Breathing

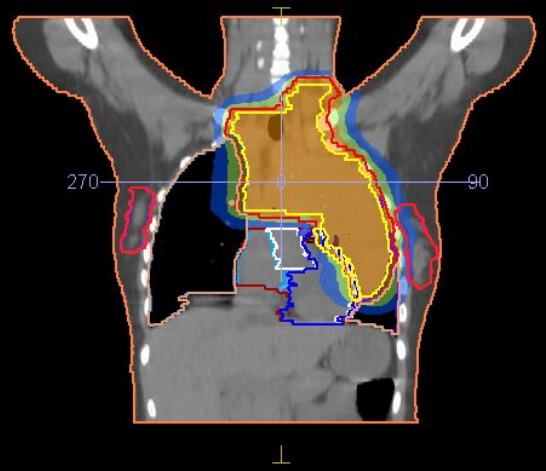
With C-PAP

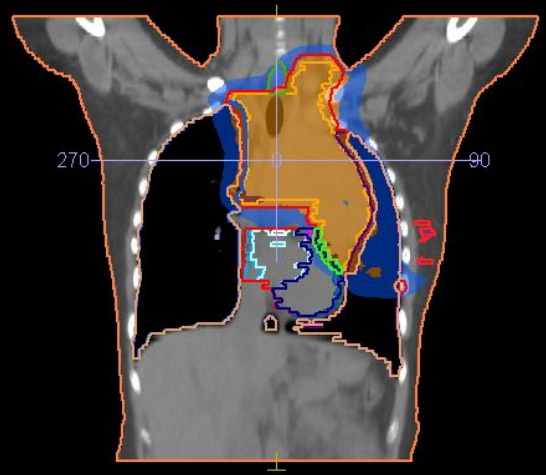
MALE PATIENT





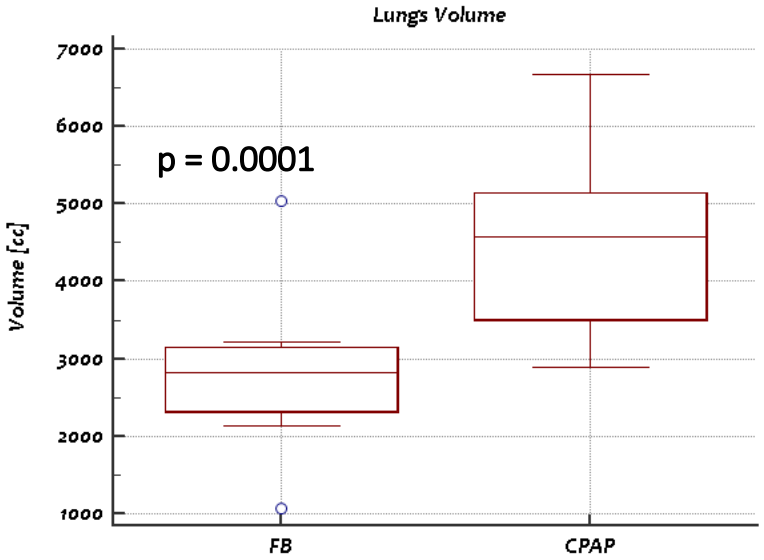
FEMALE PATIENT



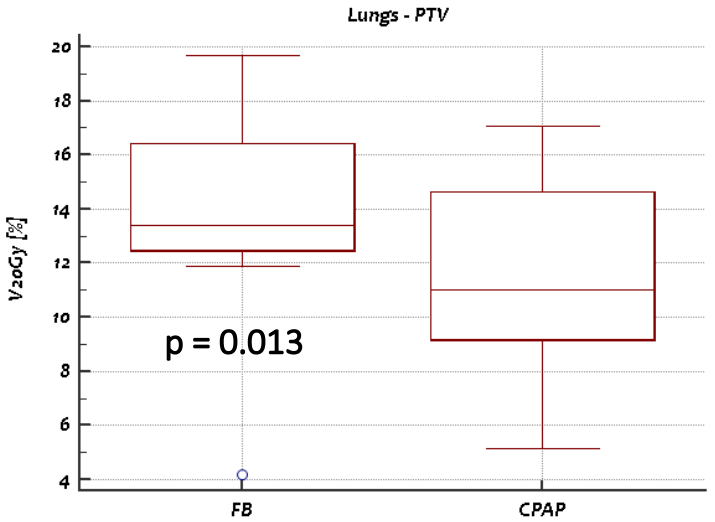


DOSIMETRIC COMPARISON (Lungs)

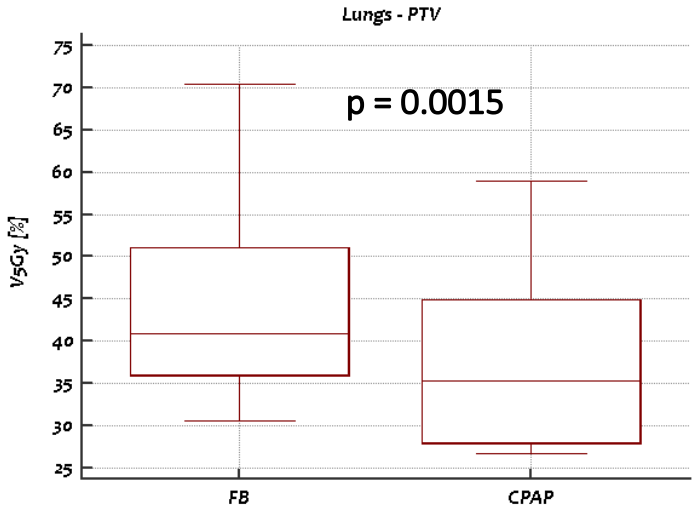
Lungs Volume



Lungs V20



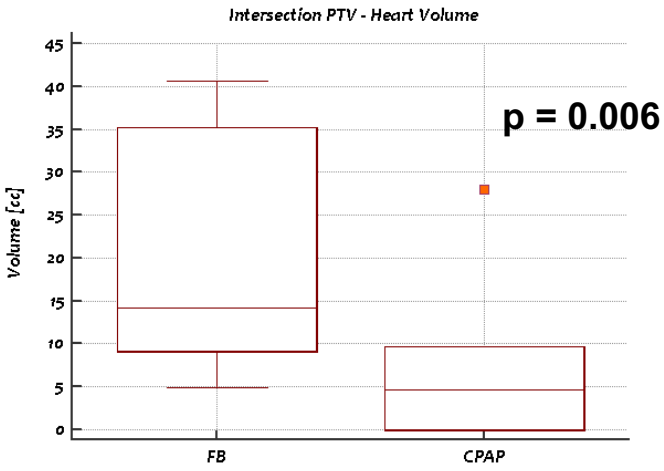
Lungs V5



10 patients included in this preliminary analysis

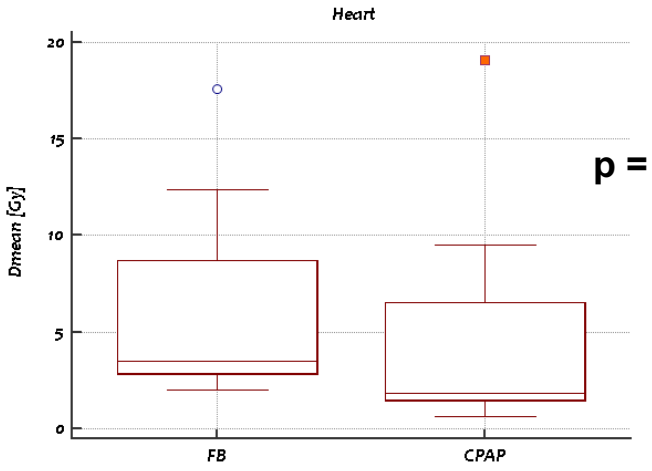
DOSIMETRIC COMPARISON (Heart)

Intersection PTV/Heart (cc)



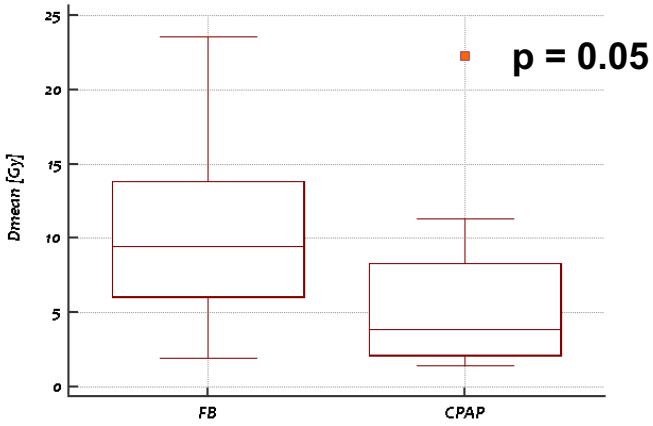
p = 0.006

Mean Heart Dose (Gy)



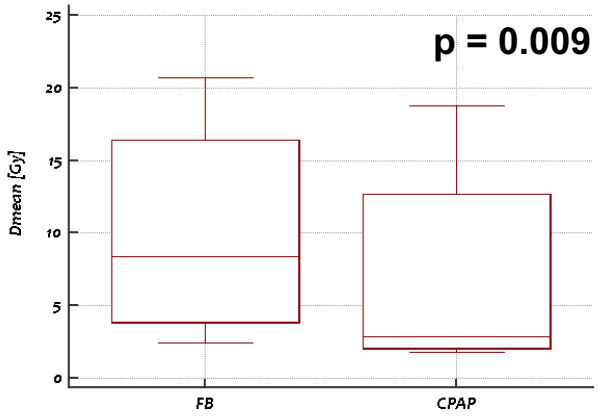
p = 0.046

Aortic Valve (mean dose)



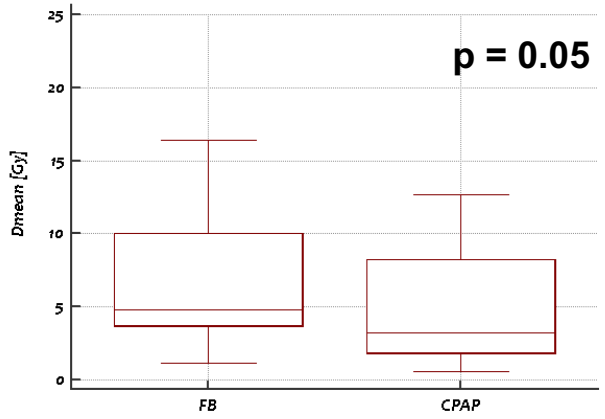
p = 0.05

Circumflex (mean dose)



p = 0.009

Left descending (mean dose)



p = 0.05

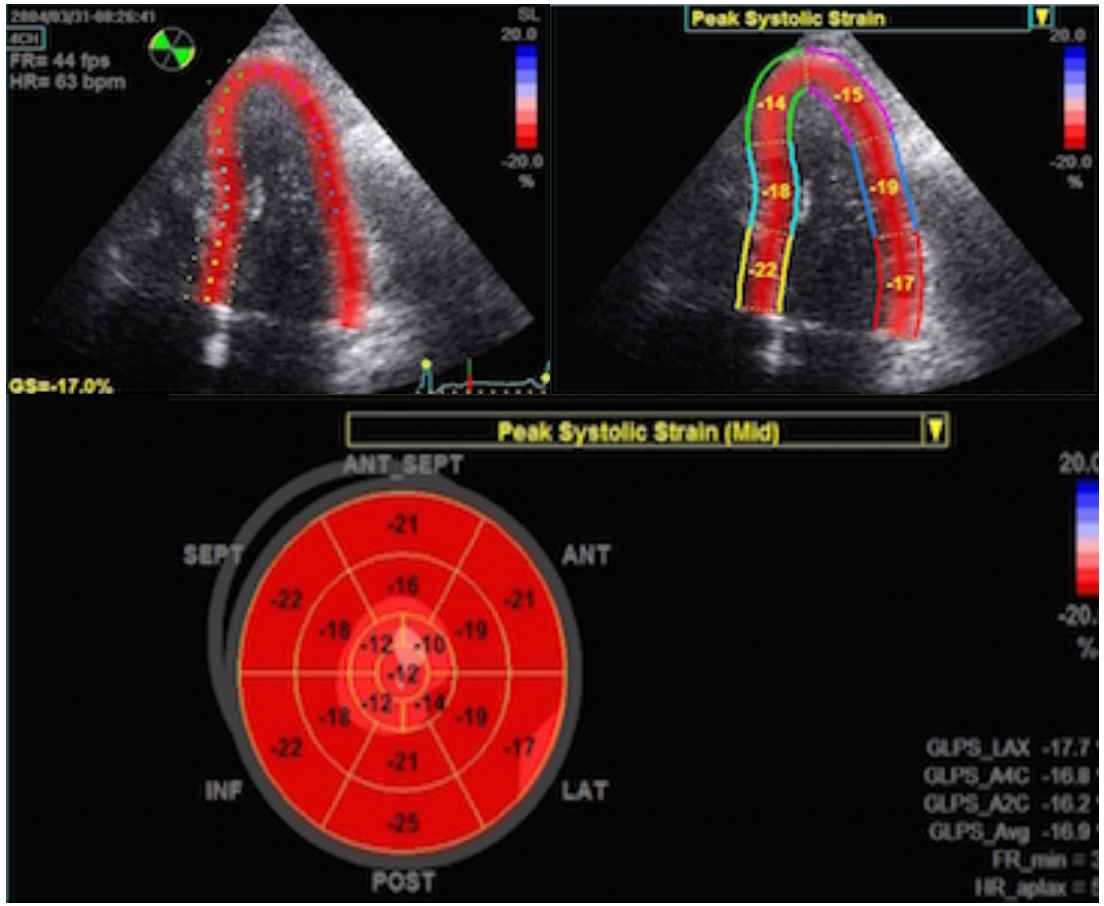
4

EARLY DIGNOSIS OF SUBCLINICAL "RIHD"

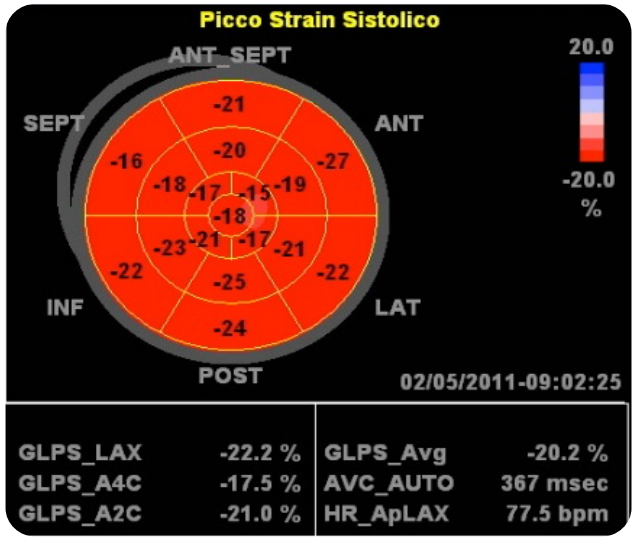
THE ”ONE MILLION DOLLAR” QUESTION

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

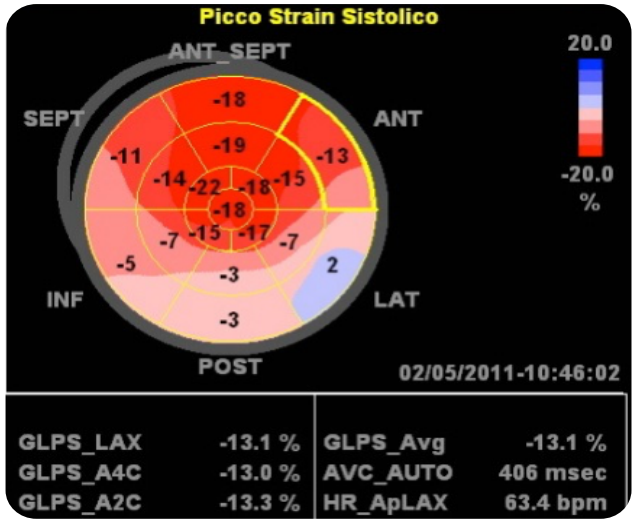
Advanced Ultrasound Imaging
2D Global Longitudinal Strain – “SPECKLE TRACKING”



Normal
GLS systolic peak

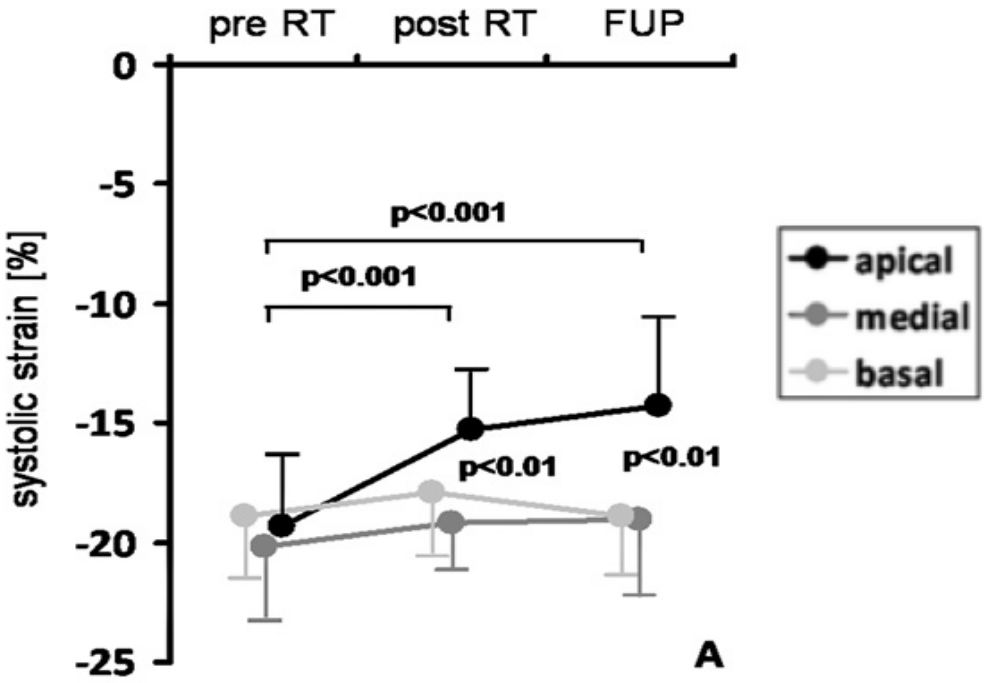


After STEMI
GLS systolic peak



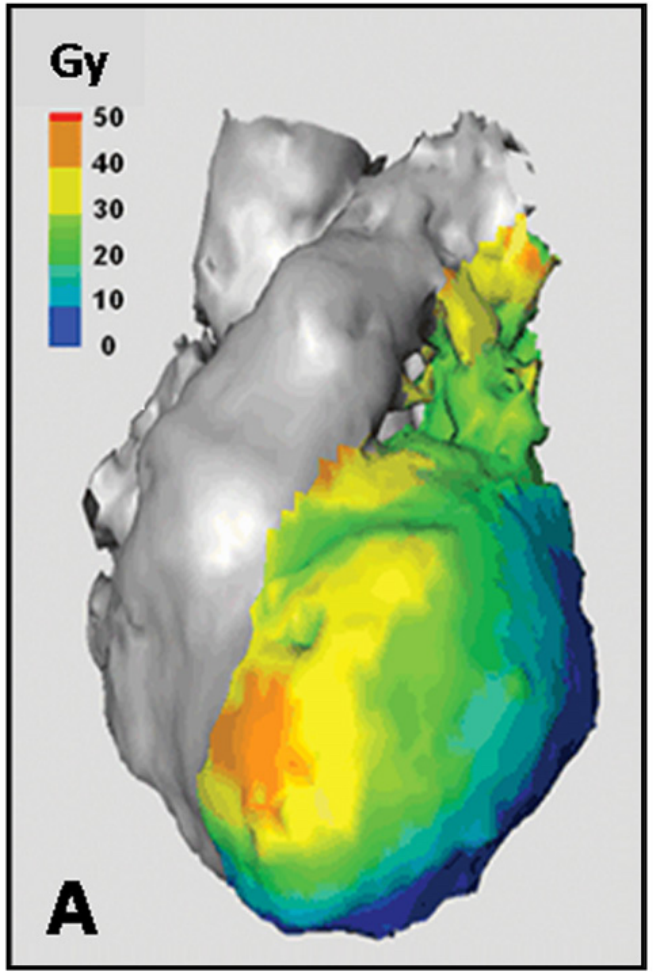
BREAST CANCER PATIENTS

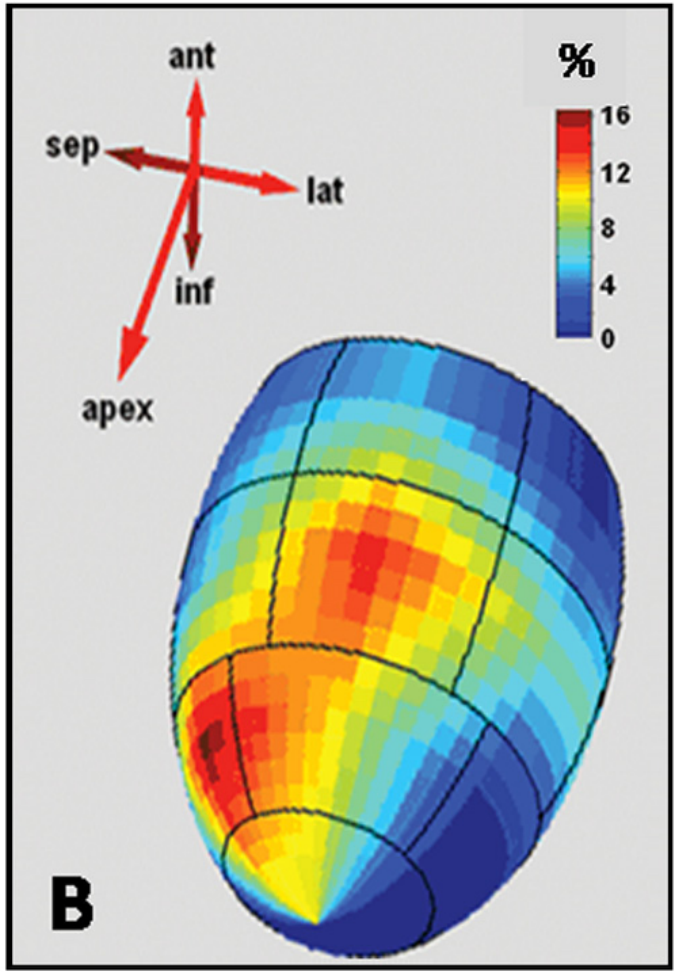
- 20 left sided and 10 right sided BC
- 50 Gy/25 fr (+/- 16 Gy boost)
- Left Ventricle Mean dose:
  A) apex 12.8 Gy; B) mid-cavity 5.4 Gy; C) base 4.5 Gy



Advanced Echocardiographic tools:

Global Longitudinal Strain (GLS)





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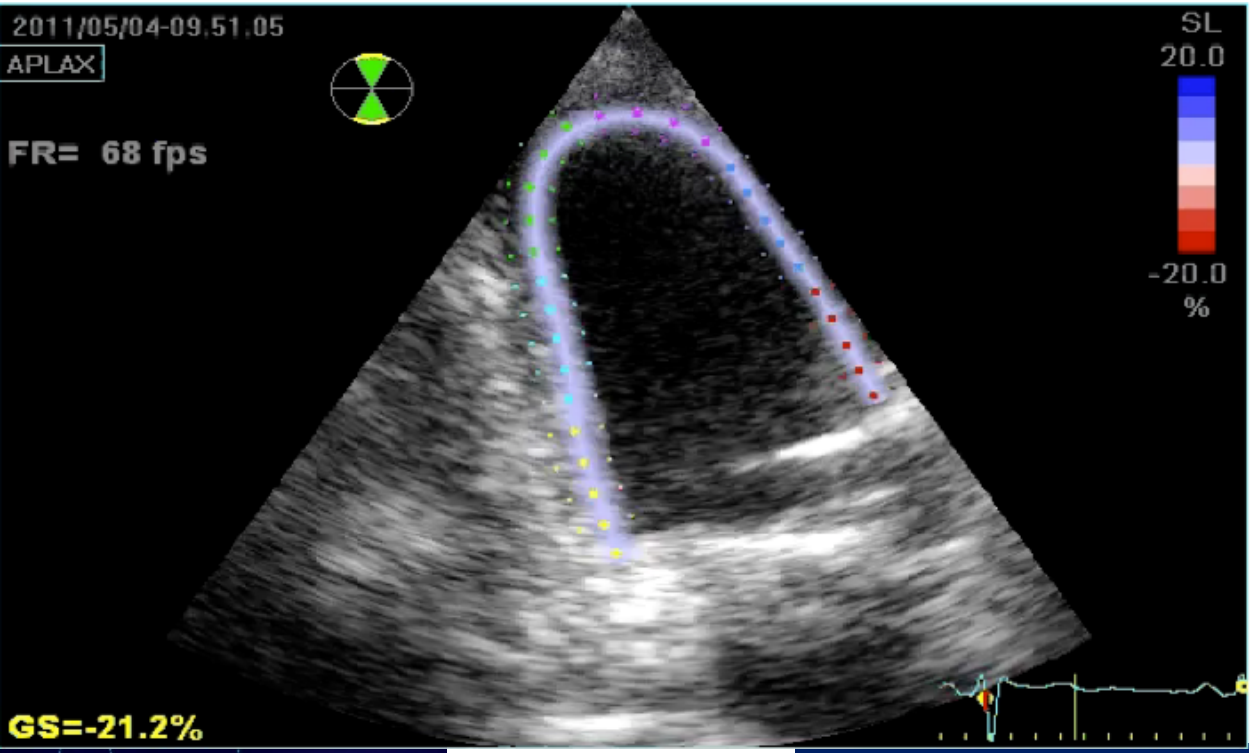
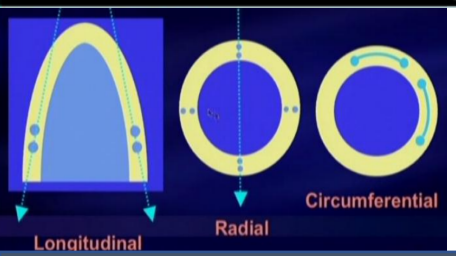
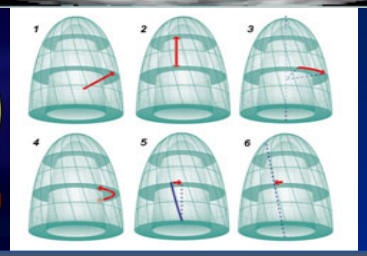
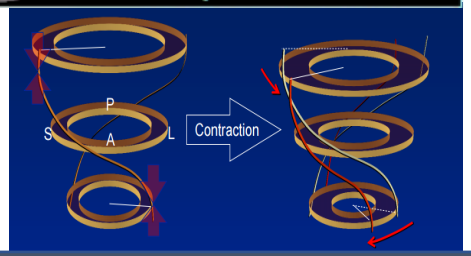
CARDIOCARE Project @ University of Torino









***Aim**: To evaluate with GLS (Global longitudinal strain) early and subclinical chemo/radiation-induced heart alterations in patients affected with HL, DLBCL or PMBCL*

CARDIOCARE Project
University of Torino

Cohort A: CHEMOTHERAPY ALONE

50 Patients
(HL – DLBCL – PMBCL)

Baseline STRAIN-Echo

CHEMOTHERAPY
Anthracycline containing regimen

Post-CT STRAIN Echo

FOLLOW UP 3 MONTHS

FINAL STRAIN Echo

Cohort B: COMBINED MODALITY TREATMENT

50 Patients
(HL – DLBCL – PMBCL)

Baseline STRAIN Echo

CHEMOTHERAPY
Anthracycline containing regimen

Post-CT STRAIN Echo

MEDIASTINAL ISRT

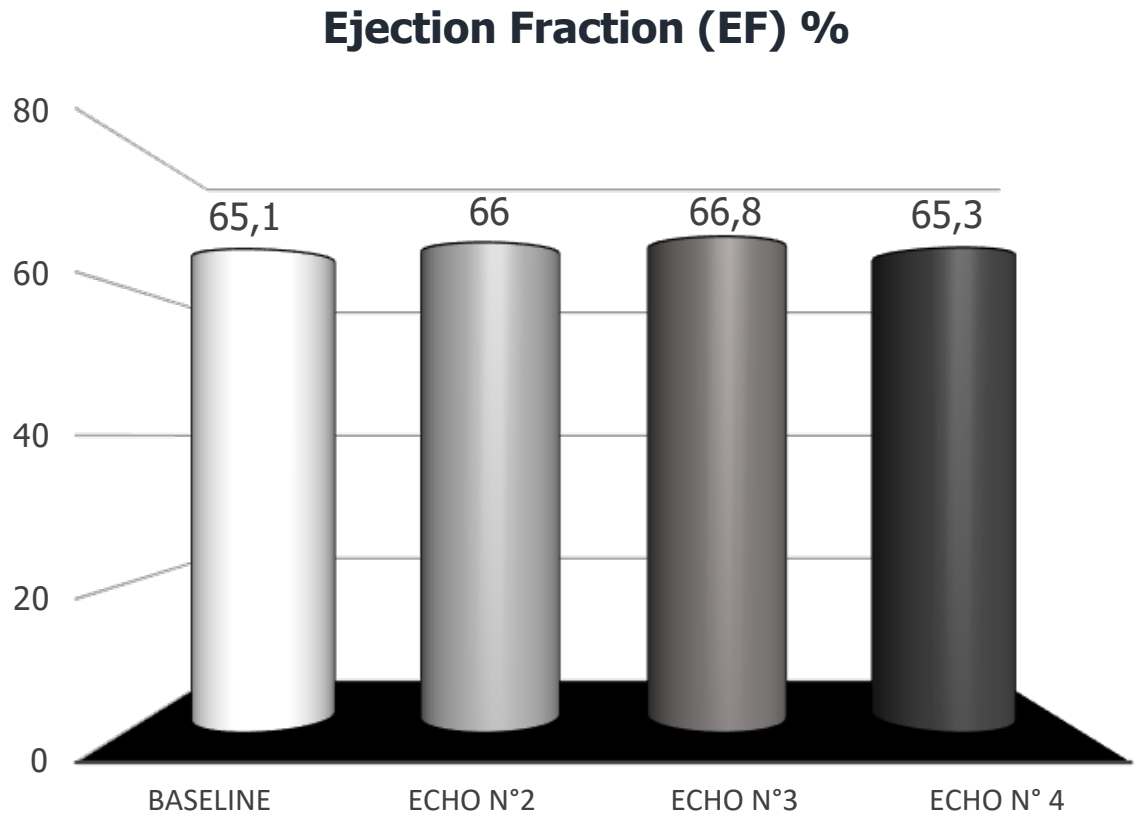
Post-ISRT STRAIN Echo

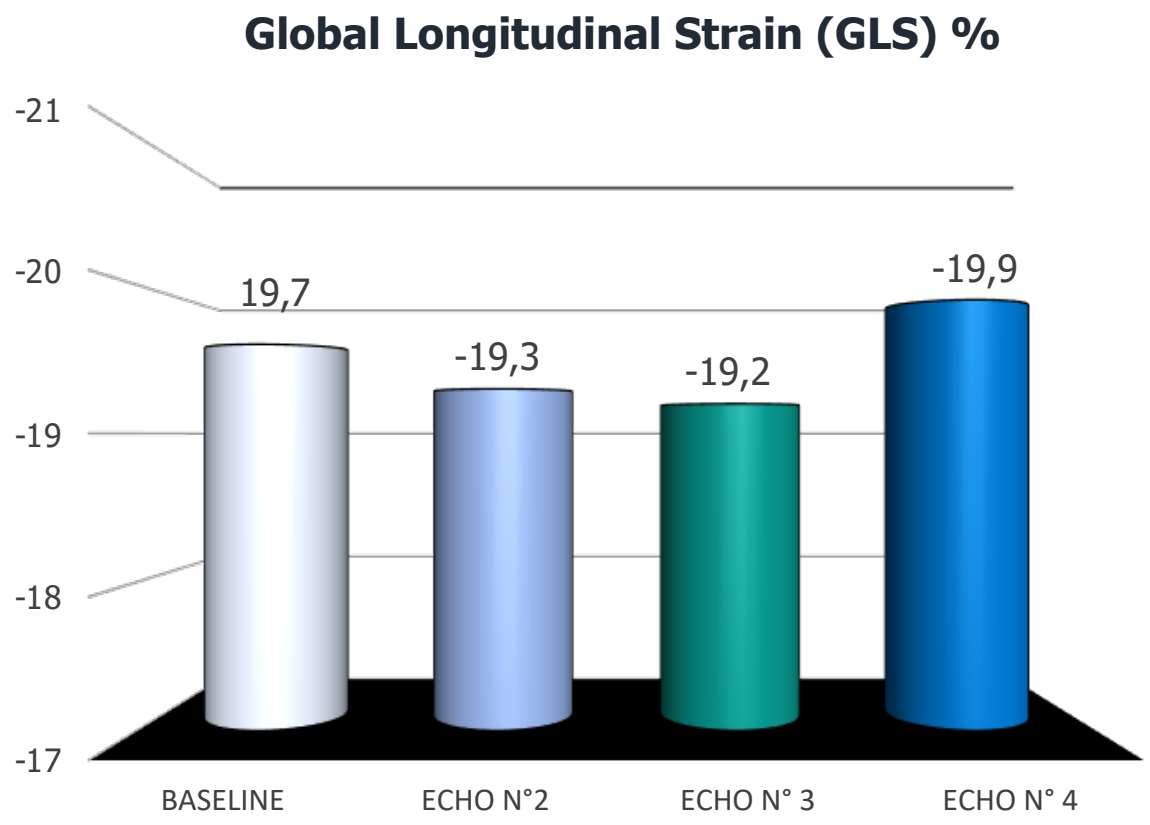
FOLLOW UP 3 MONTHS

FINAL STRAIN Echo

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

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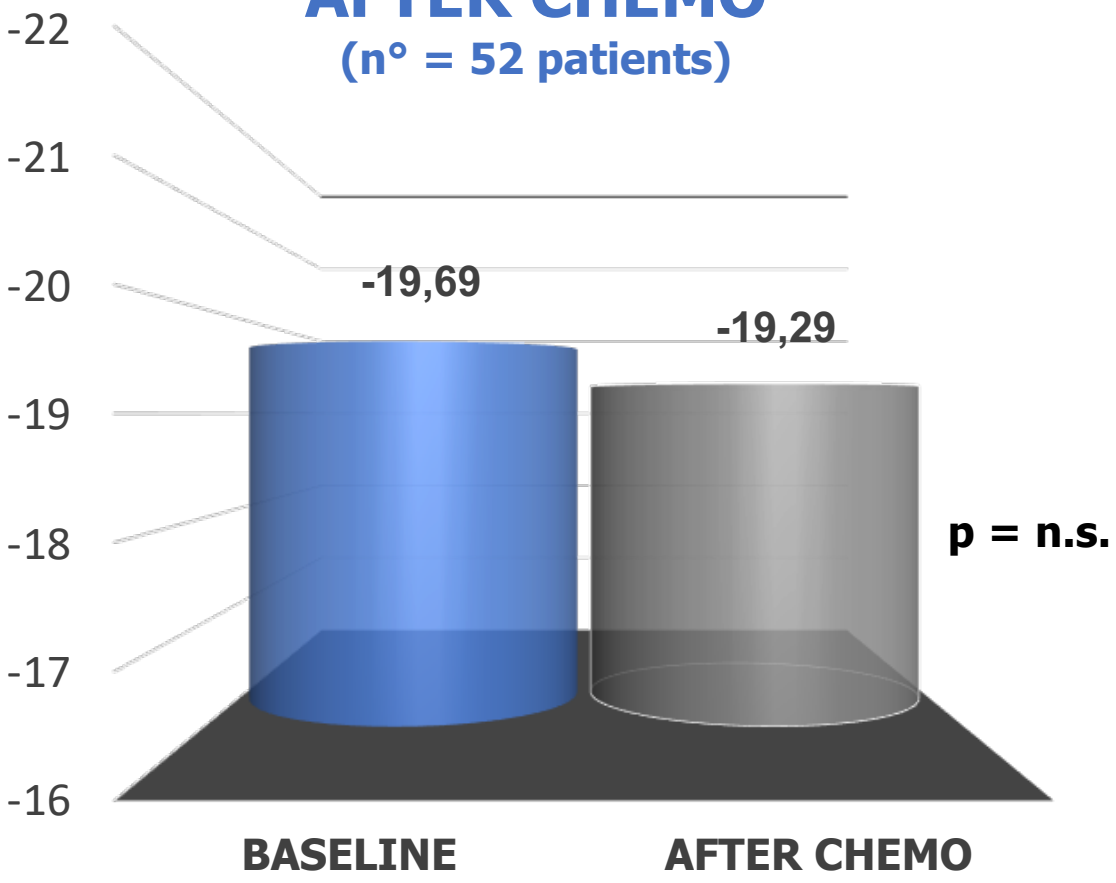
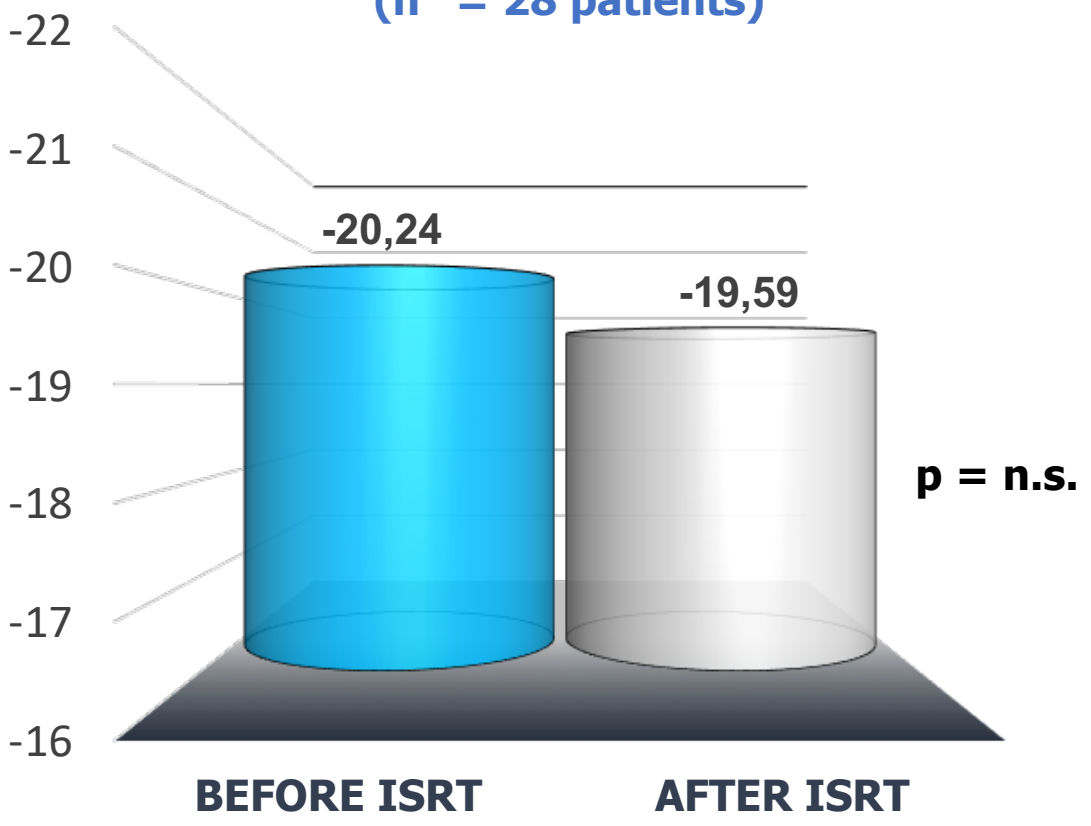
RESULTS – OVERALL POPULATION
(GLS reduction after treatments)

AFTER CHEMO
(n° = 52 patients)



AFTER ISRT
(n° = 28 patients)



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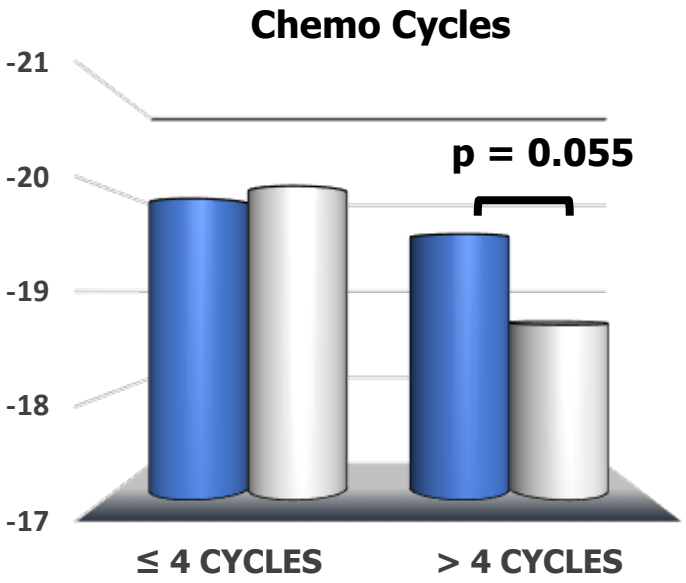
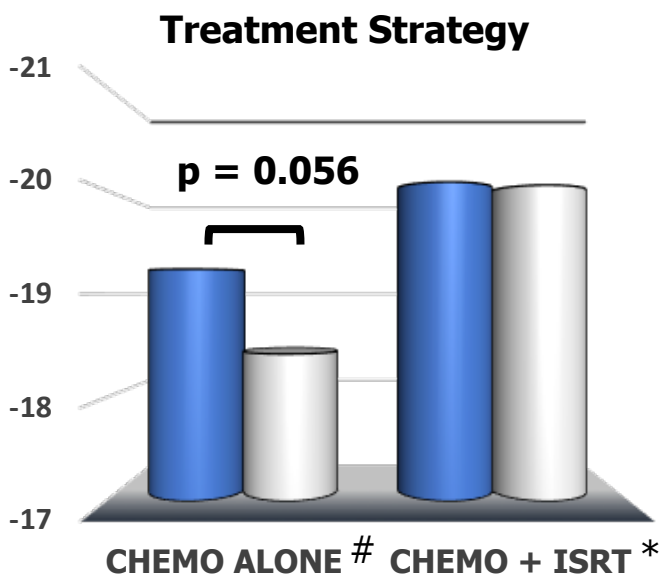
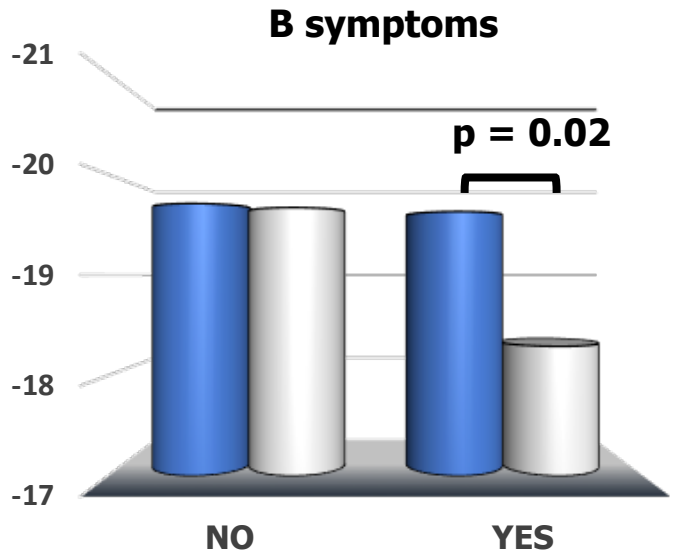
RESULTS
(GLS changes after chemo)
Subgroup analysis

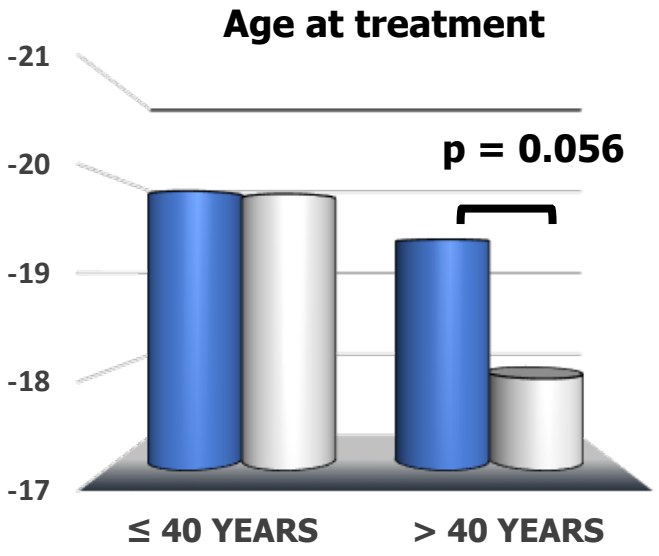


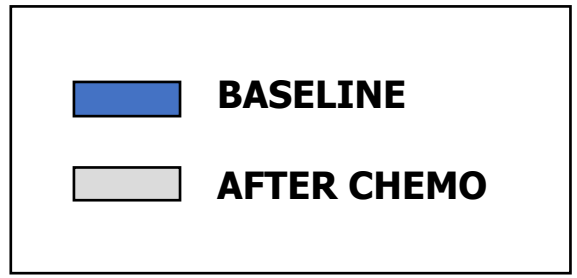


median anthracycline dose: 500 mg

* median anthracycline dose: 400 mg



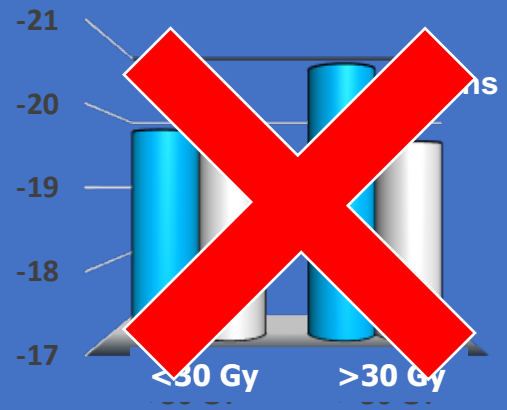
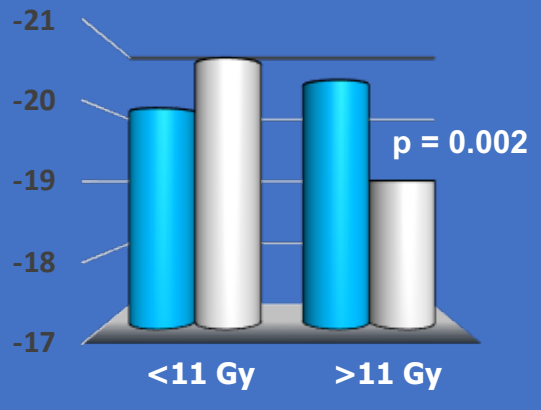
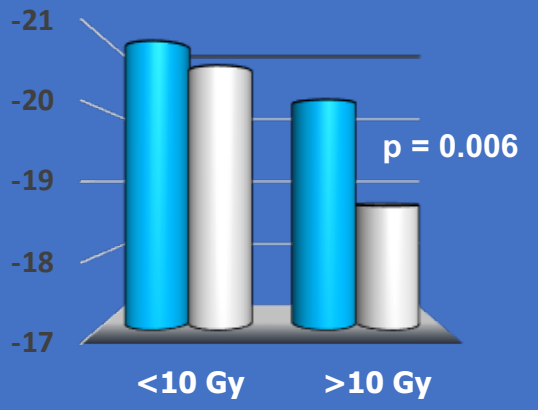
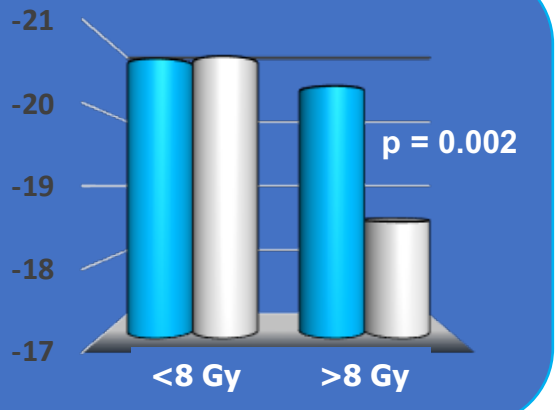
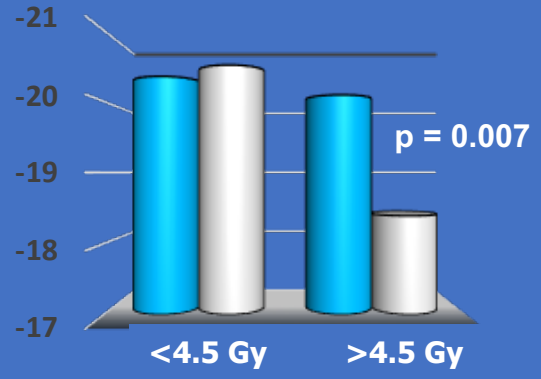
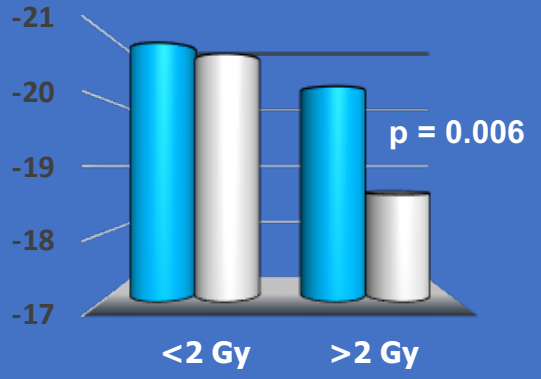
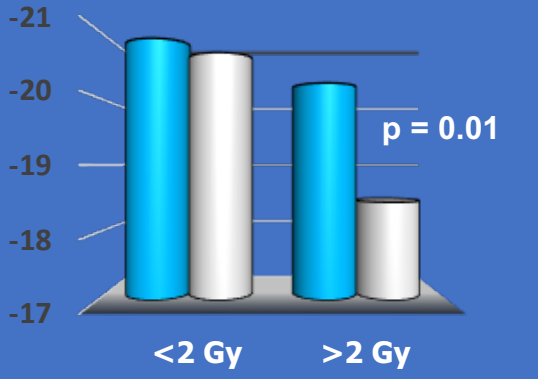
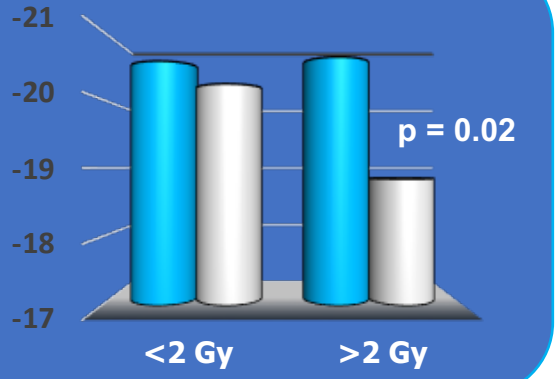




RESULTS
(GLS changes after ISRT) Subgroup analysis

BEFORE ISRT

AFTER ISRT

	Whole Heart	Left Ventricle	Interventricular Septum	Lateral Wall
Max Dose				
Mean Dose				

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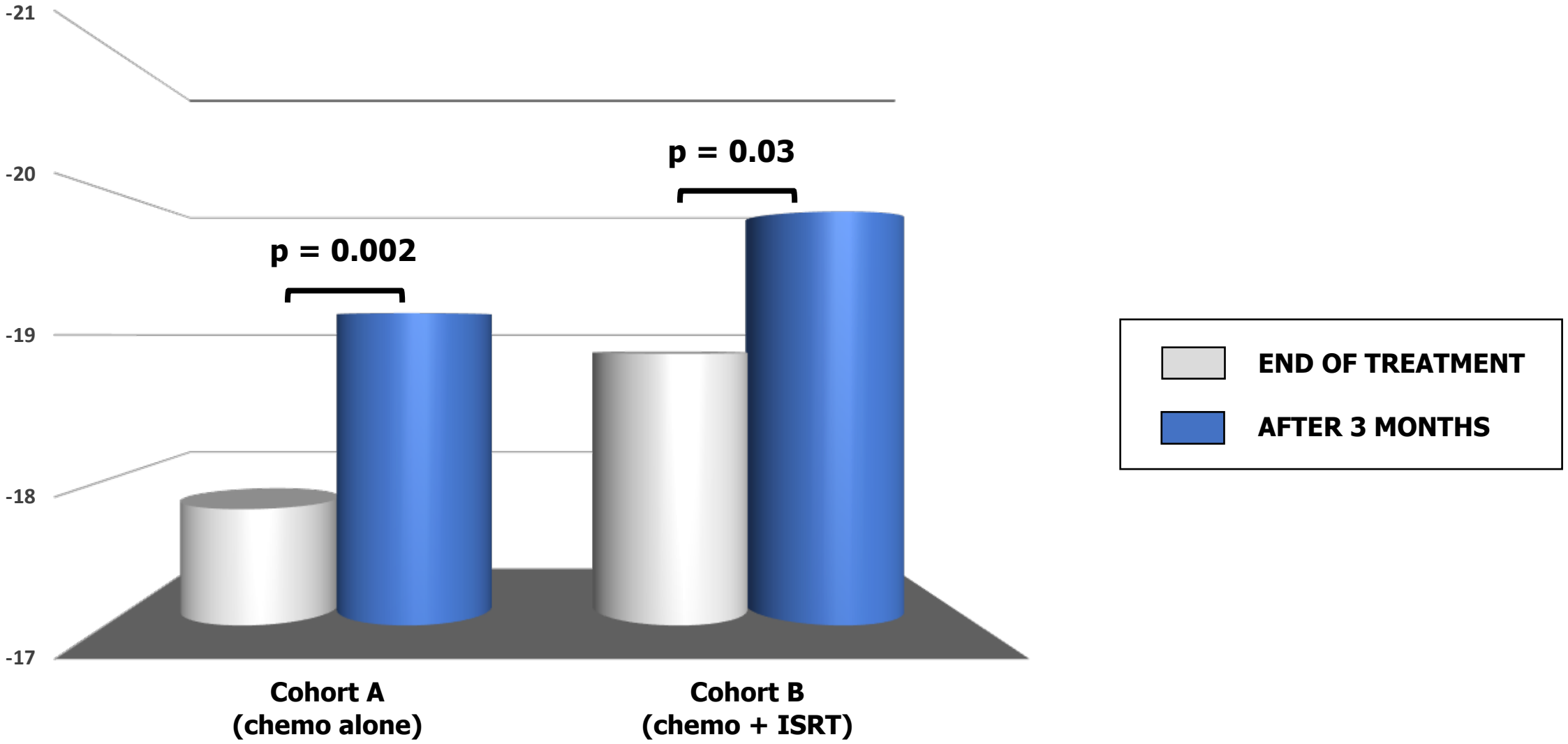
RESULTS
(GLS recovery 3 months after end of treatment)



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AKNOWLEDGMENTS

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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 and RT INDUCED heart toxicity in a PRECLINICAL PHASE


Protect Your
HEART
You
Only
Have One