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Dept. of Radiation Oncology
UF College of Medicine

Proton therapy preserves acute left ventricular ejection fraction relative to conventional X-ray therapy in breast cancer

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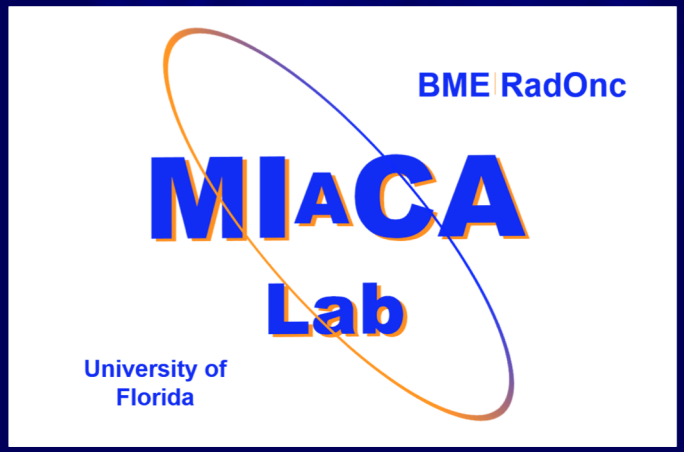

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http://odell.radonc.med.ufl.edu/MIACALab

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Key Contributors

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(now attending Stanford U.)

Use of RT in advanced BC

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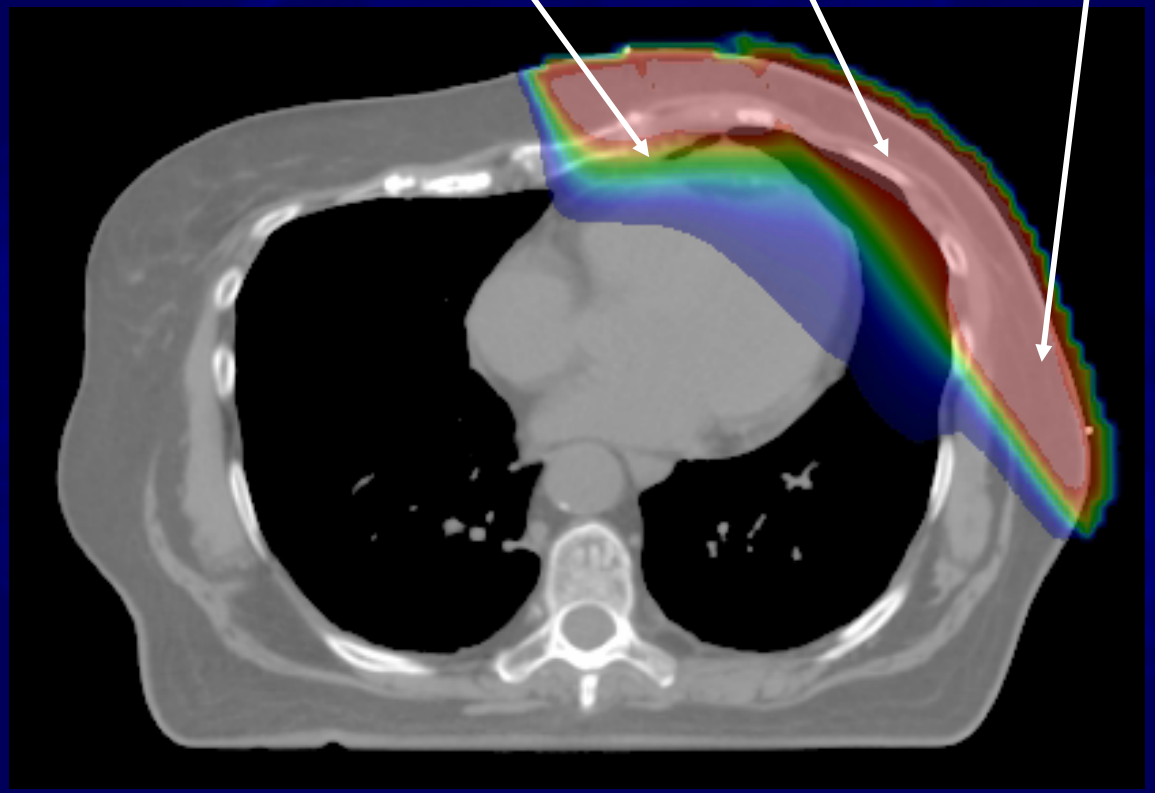
1. Over 250,000 new breast cancer diagnoses annually in US.
2. Patients with Stage II+, node-positive BC have improved overall and disease-free survival with the use of RT to the mediastinal lymph nodes, chest wall and axilla.



BC RT and cardiac injury

- Each 1 Gy heart dose increases risk of heart events by 7%[1].
- Historical mean heart dose during RT is 1-2 Gy for right-sided BC patients and 3-10 Gy for left-sided.
- Historically, BC patients with RT have a 27% increased risk of cardiac death[2].
- Patients with left-sided BC have a 56% higher risk of cardiac events than patients with right-sided BC: 28-70% vs. 7-14%[3].

1. Darby SC, Ewertz M, *et al*. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; 368: 987-98.

2. Clarke M, Collins R, *et al*. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366: 2087-106.

3. K. Bouillon, N. Haddy, S. Delaloge, *et al.*, Long-Term Cardiovascular Mortality After Radiotherapy for Breast Cancer, Journal of the American College of Cardiology **57**(4), 445–452 (2011)

central park
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X-rays versus protons

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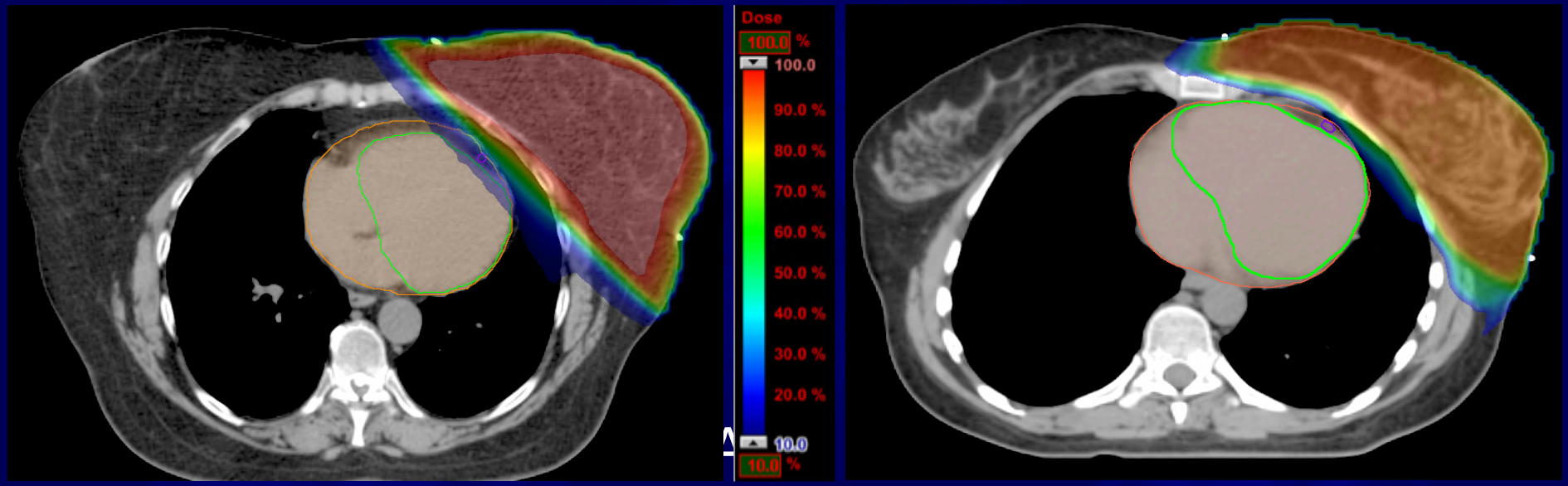

Comparison of breast RT treatment plans when using X-rays versus protons. [A] is a radiation treatment plan using conventional X-rays. [B] is a plan using protons. The rainbow color overlay represents the spatial dose distribution with red being high dose. Both plans are designed to irradiate the breast, chest wall, axillary and mediastinal lymph nodes. Dosimetrically, the proton treatment plan results in less volume of heart receiving high dose.

National Trials

Proton Collaborative Group: NCT01758445 *Proton Radiation for Stage II/III Breast Cancer*
Endpoint: incidence of cardiac mortality at 10 and 15 years following PT.
Expected completion date: January, 2030

NCT02603341 *Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial.*
Endpoint: incidence of major clinical cardiac events between PT & CRT.

Limitations:

- Endpoints are major cardiac events (binary yes/no) rather than graded measures of the severity of toxicity and effect on QOL.
- Require 10+ year assessment.

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UF-PTI study

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UFPTI BR02: Prospective Pilot Study of Early Markers of Radiation-Induced Cardiac Injury in Patients with Left-Sided Breast Cancer Receiving Photon or Proton Therapy

Julie Bradley[1], Walter O'Dell, Christopher Klassen[2]

[1]Radiation Oncology, UFPTI, Jacksonville FL

[2]Radiology UFH Shands Hospital, Jacksonville FL

Funded by the Ocala Royal Dames for Cancer Research

Endpoint: quantify the incidence and severity of early, sub-clinical cardiac toxicity using MRI and compare PT vs CRT.

Goals:

i. Better understand the sequela of events leading to heart failure.

ii. Identify patients needing more active follow-up heart care.

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Heart MRI for global heart function

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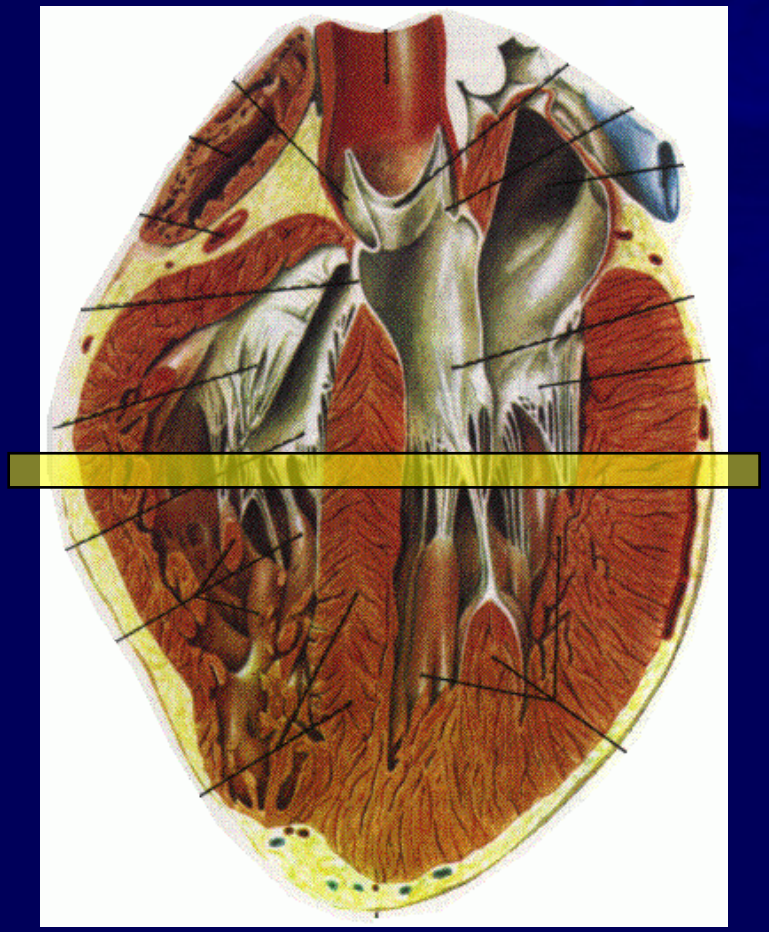
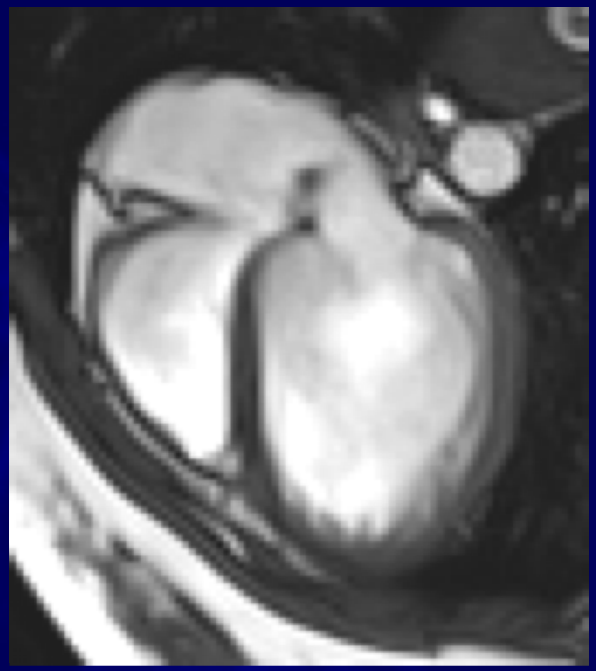
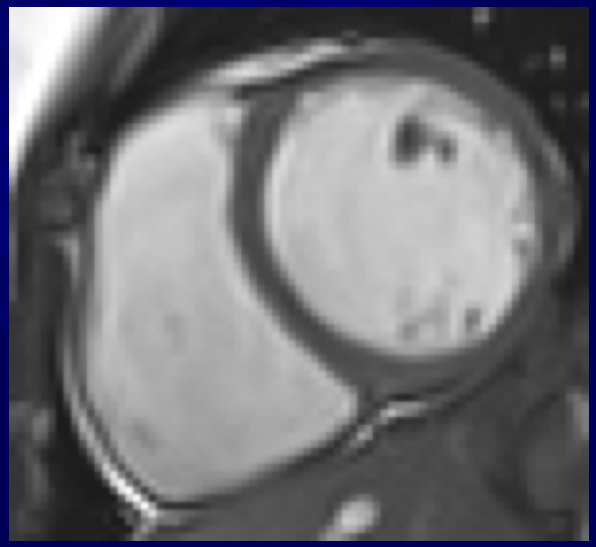


Long-axis view



Short-axis view



Imaging heart function

Anatomical information

-- congenital abnormalities

-- wall thickness

-- myocardial mass

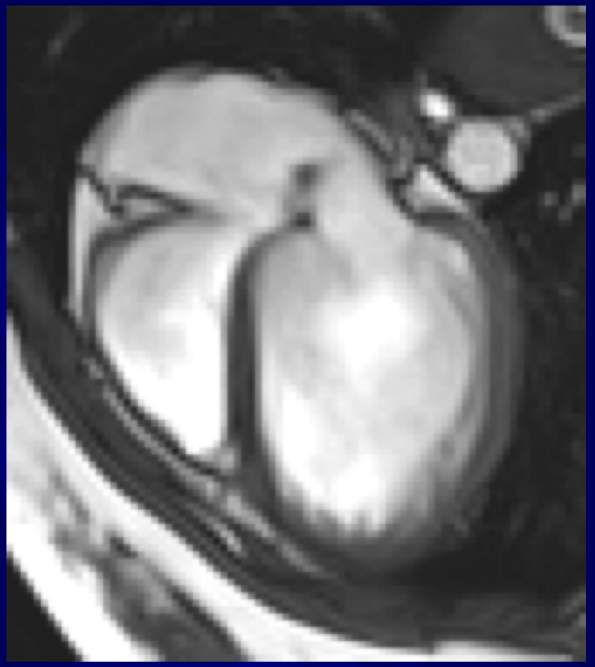
Heart Pump Function

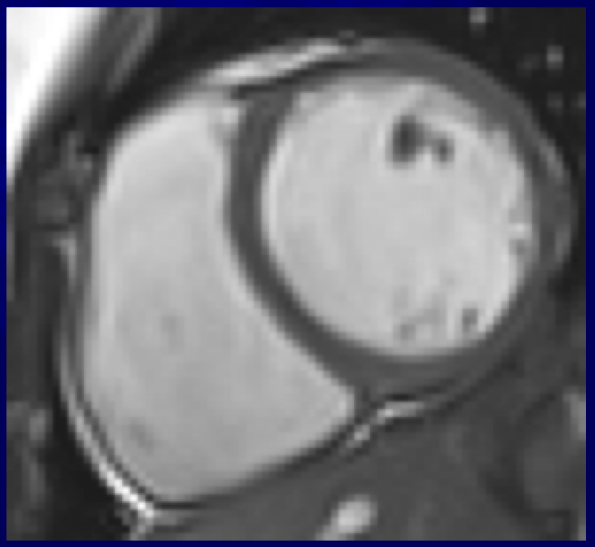
cardiac output = stroke volume* HR

ejection fraction (EF) =

stroke volume/end-diastolic volume

LVEF is the most commonly-used clinical measure of heart mechanical function

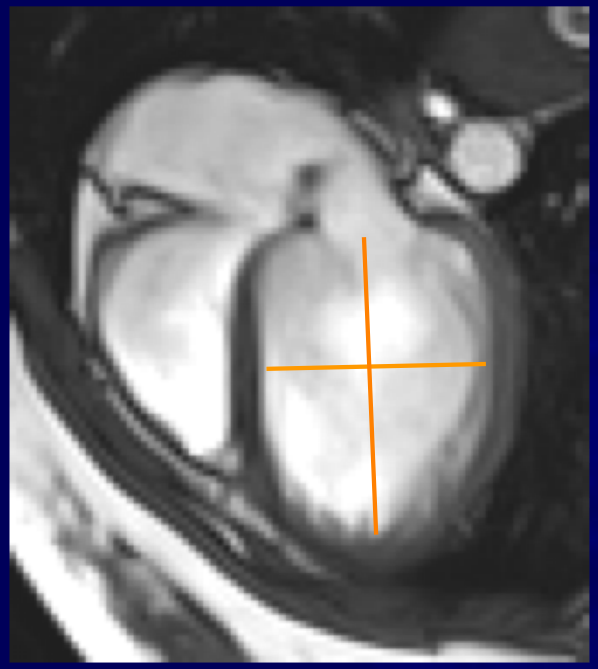


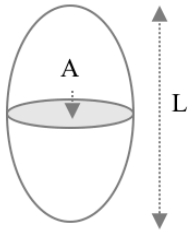
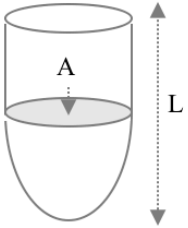
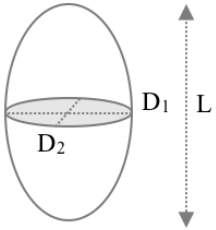
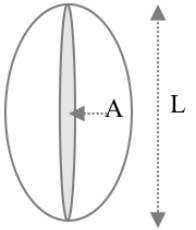
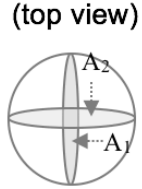


Estimating LV Volume and EF

Commonly-used methods for computing LVEF in the clinic:

- Using only short-axis slices: Composite Mid-point Integration Method (aka Simspon's rule), Wyatt's modified-Simpson method
- Using only 1 or 2 dimensions in a single long-axis view: Dodge, Teichholz



A	B	C	D	E
				
Bi-plane ellipse	Bullet	3-axis measurement	Single plane long-axis ellipse	Bi-plane long-axis ellipse
$V = \frac{2}{3}AL$ (3)	$V = \frac{5}{6}AL$ (4)	$V = \frac{\pi}{6}D_1D_2L$ (5)	$V = \frac{8}{3\pi}\frac{A^2}{L}$ (6)	$V = \frac{8}{3\pi}\frac{A_1A_2}{L}$ (7)

- These geometric models are overly-simplistic, leading to >15% error in LVEF.
- This large error would mask the small early changes in LVEF of interest.
- Need to combine multi-slice, multi-planar data into a 3D geometric model.

3D Imaging

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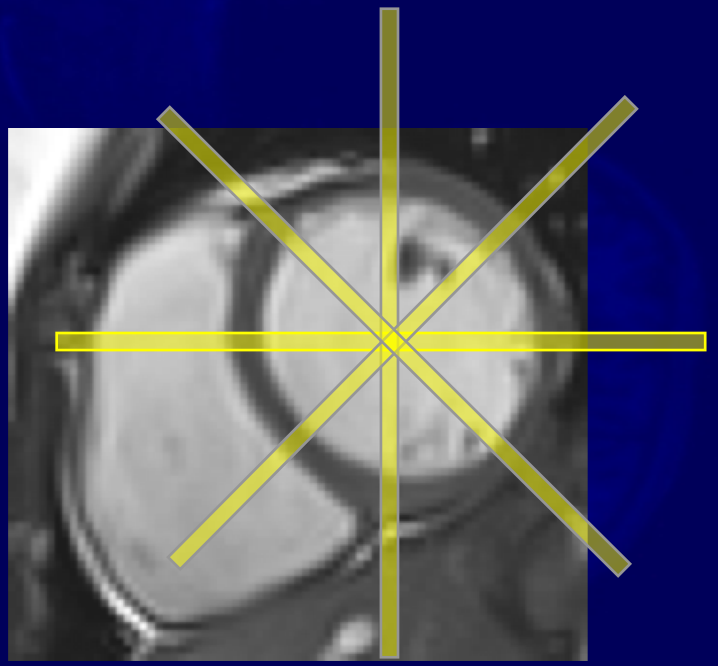
Goal:

i. Sample the LV surface in 3D.

ii. Clearly view the mitral valve orifice and the full apical extent of the LV at all time frames.



3D Imaging

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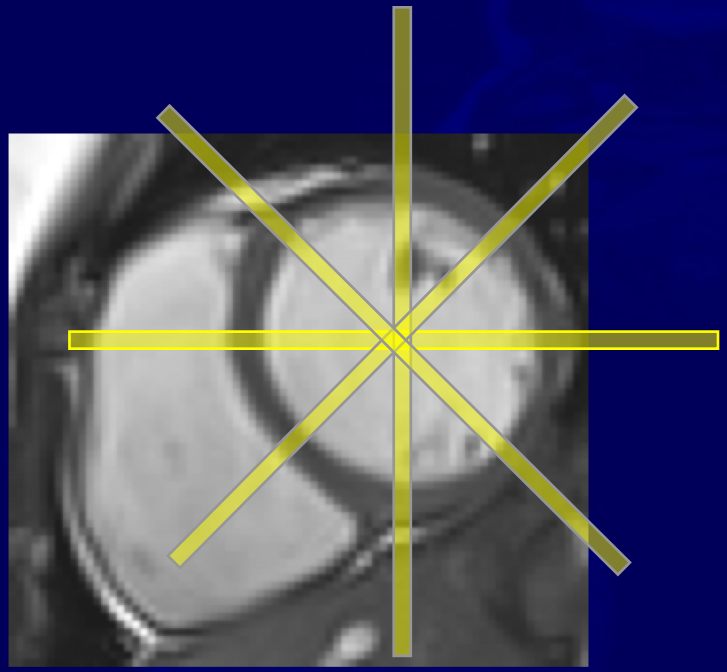
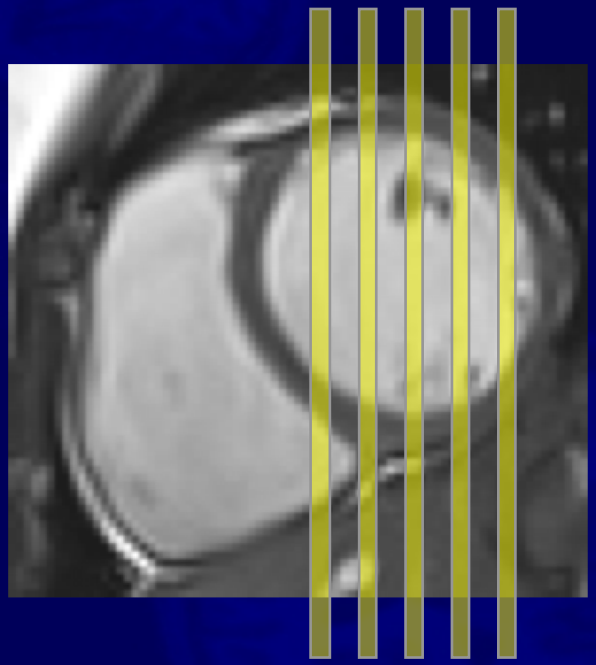
Radial
Long-axis images
(preferred)



Parallel
Long-axis images



Contour surface fitting

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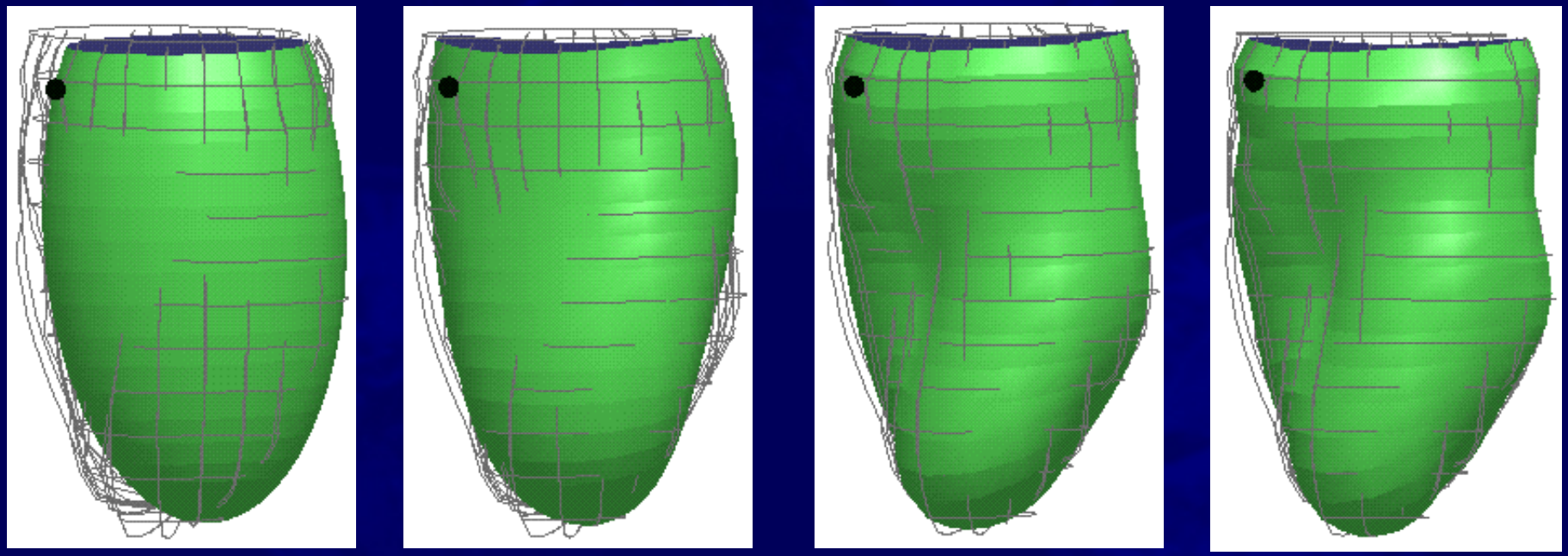
surface model:

$$\lambda(\mu,\theta) = \sum_{l=0}^{L} \sum_{m=-l}^{l} a_i P_l^{|m|}(\cos\mu) \cdot \begin{cases} \sin m\theta & m > 0 \\ \cos m\theta & m \le 0 \end{cases}$$

number of terms: 1 9 36 100



Human heart endocardial (inside) surface:
Lines are contour points from an MRI dataset and the green surface is the model representation.
The number of terms in the model increases from left to right.

Left ventricular volumes

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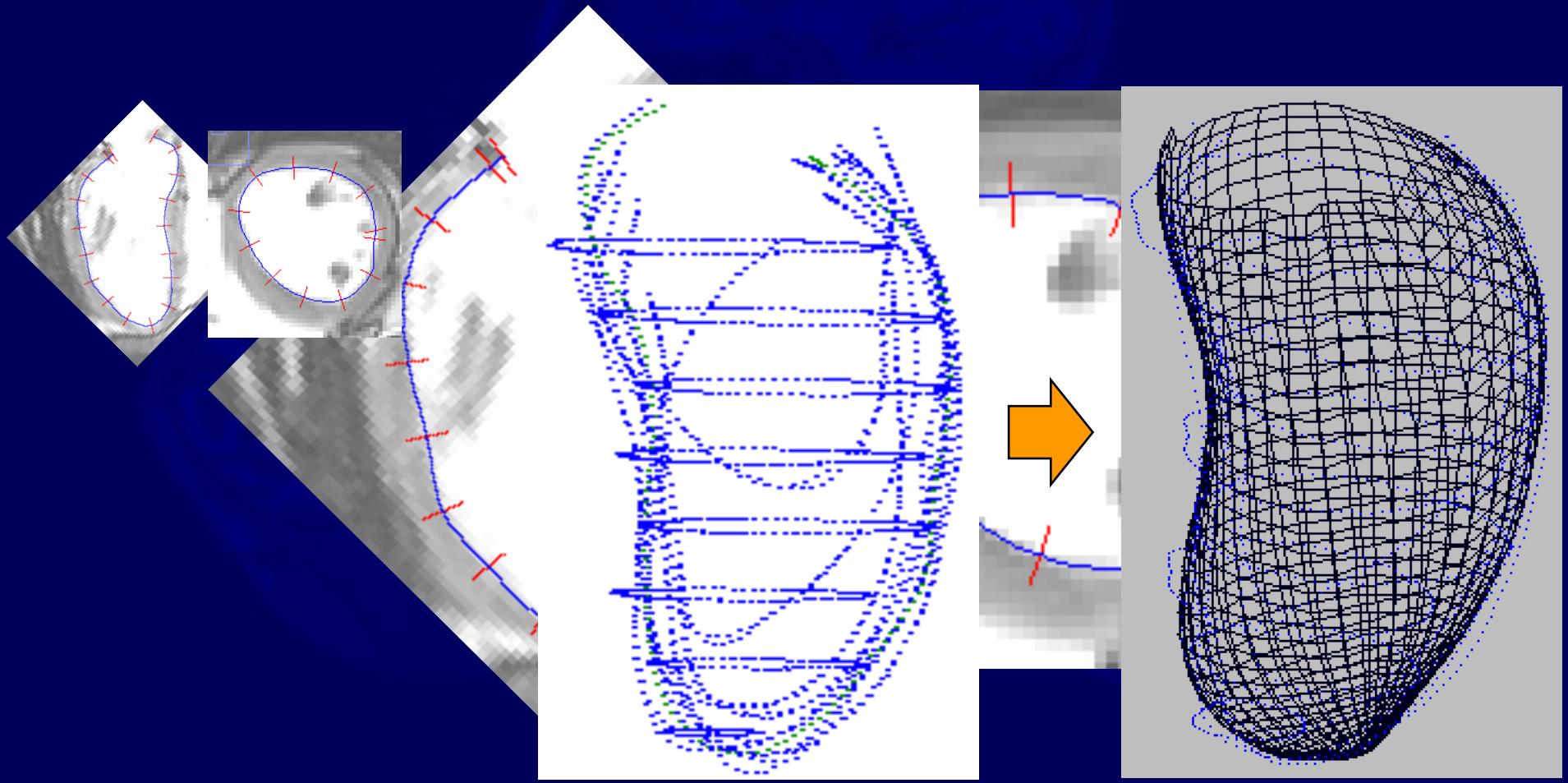
1: Acquire images over multiple locations and views.

2: Segment LV at each slice and time.

3. Combine views & slices into a 3D mathematical model of the LV.



Left ventricular volumes

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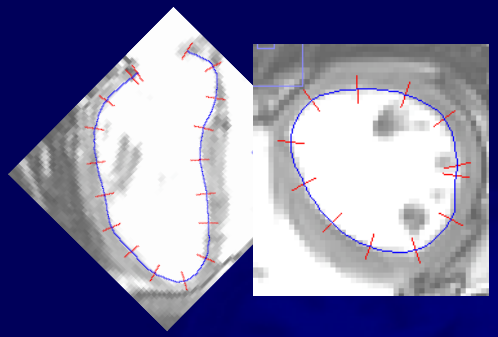
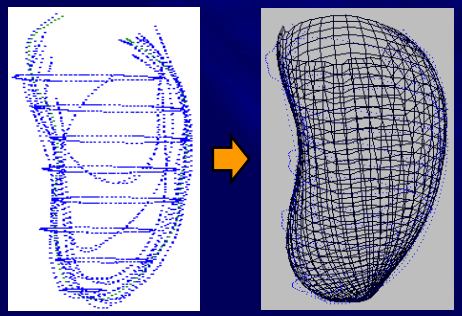
1: Acquire images over multiple locations and views.

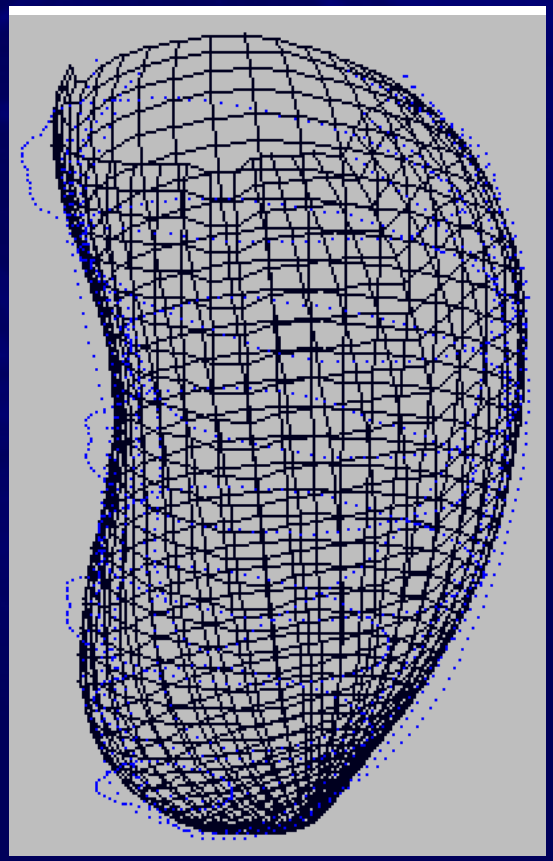
2: Segment LV at each slice and time.

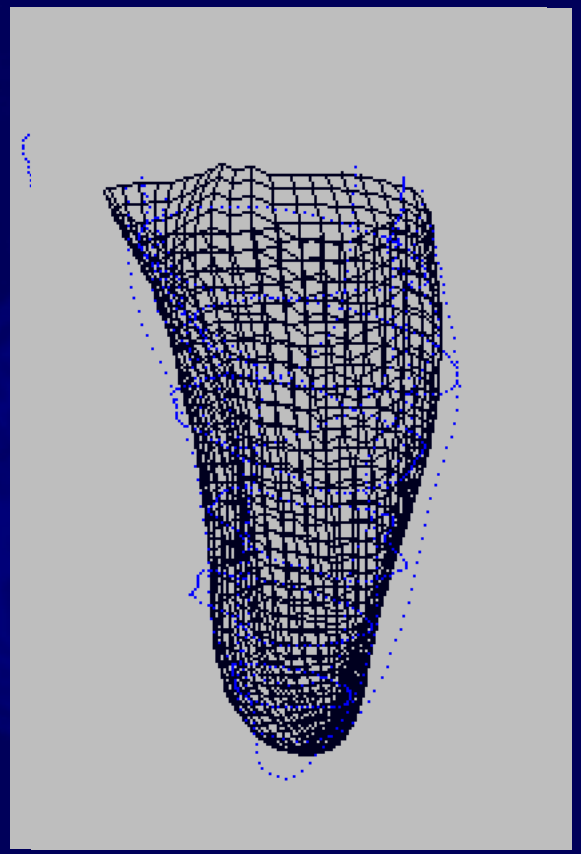
3. Combine views & slices into a 3D mathematical model of the LV.

4. Quantify LV volumes and ejection fraction from the 3D models.









Validating LV Volume

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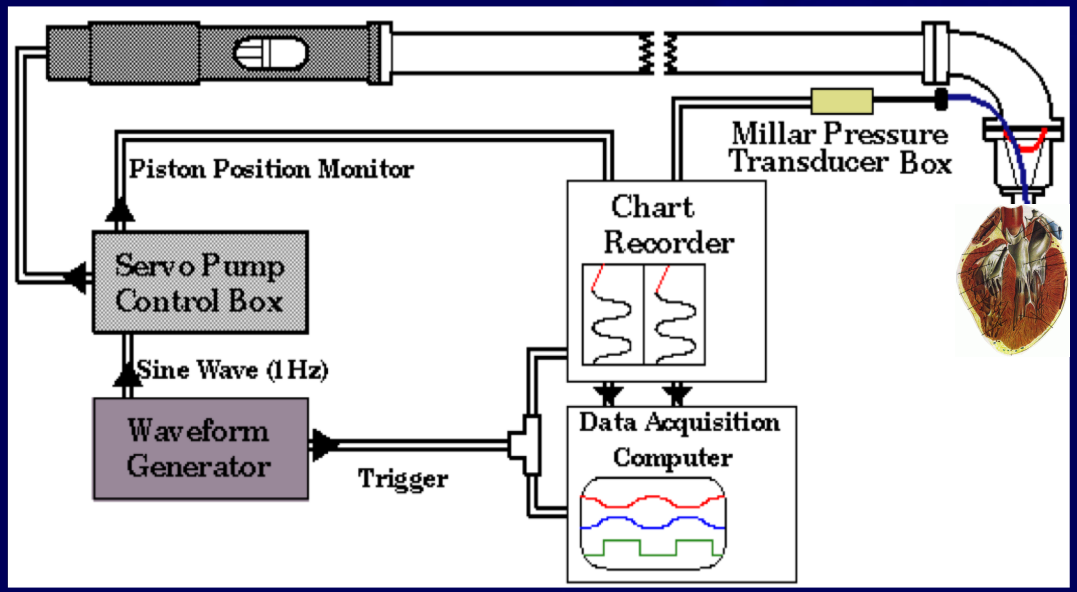
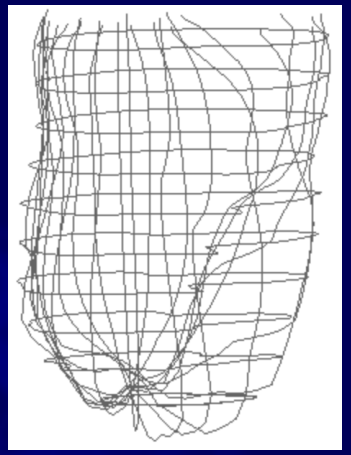
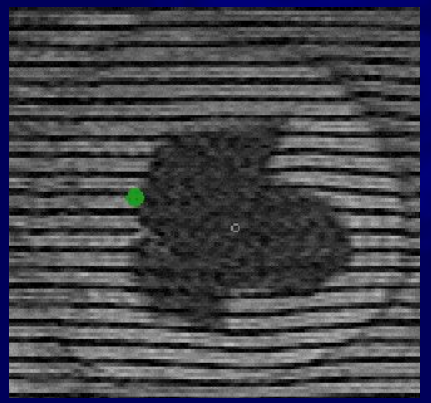
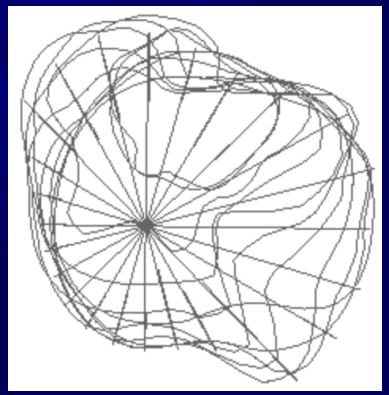
Isolated canine heart MRI study

- Balloon surgically inserted into LV at end of water column.
- Computer-controlled LV volume excursion via servo pump.
- H_3O in balloon for contrast.
- 12 short-axis and 12 long-axis image slices.
- 14 time frames.









Estimating LV Volume

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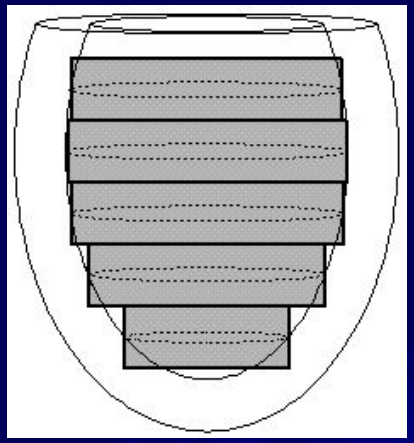
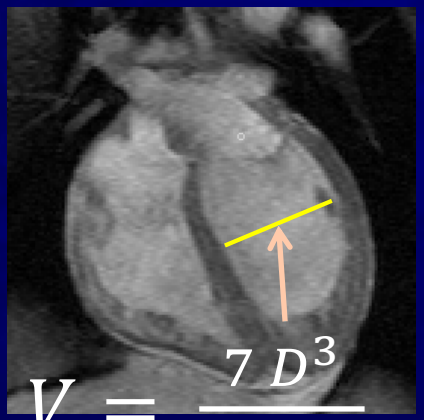
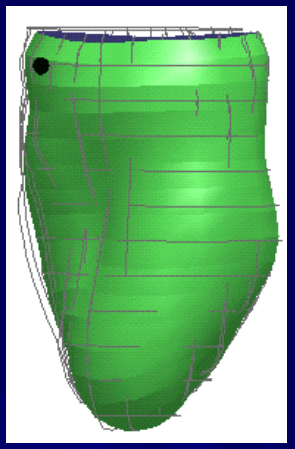
Wyatt Method

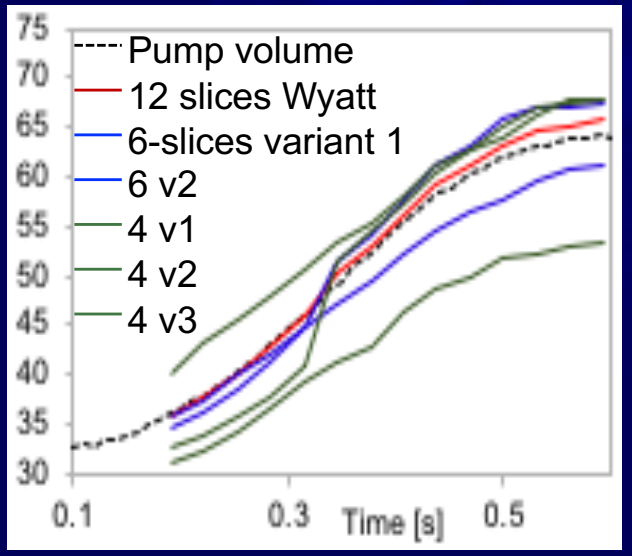


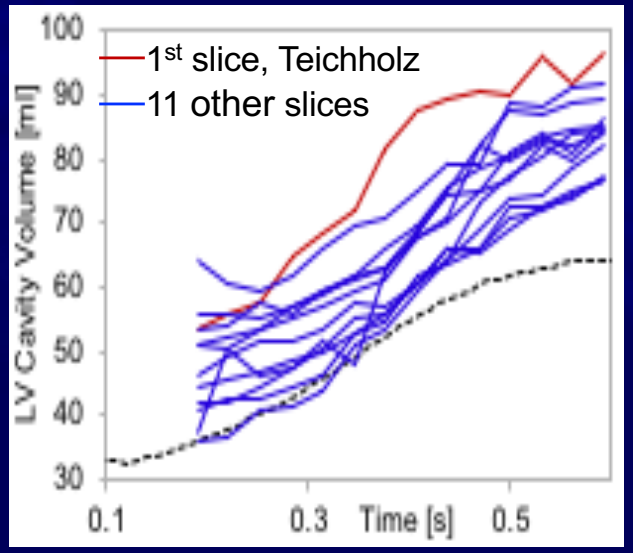
Teichholz Method

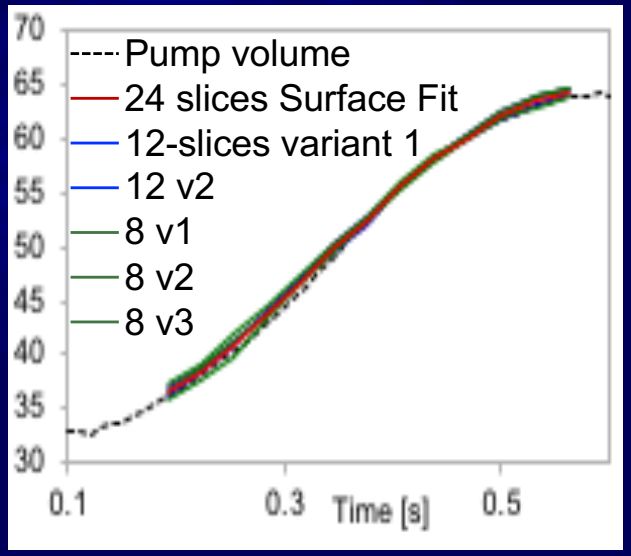


3D Modelling Method









ΔLVEF pre- vs post-RT

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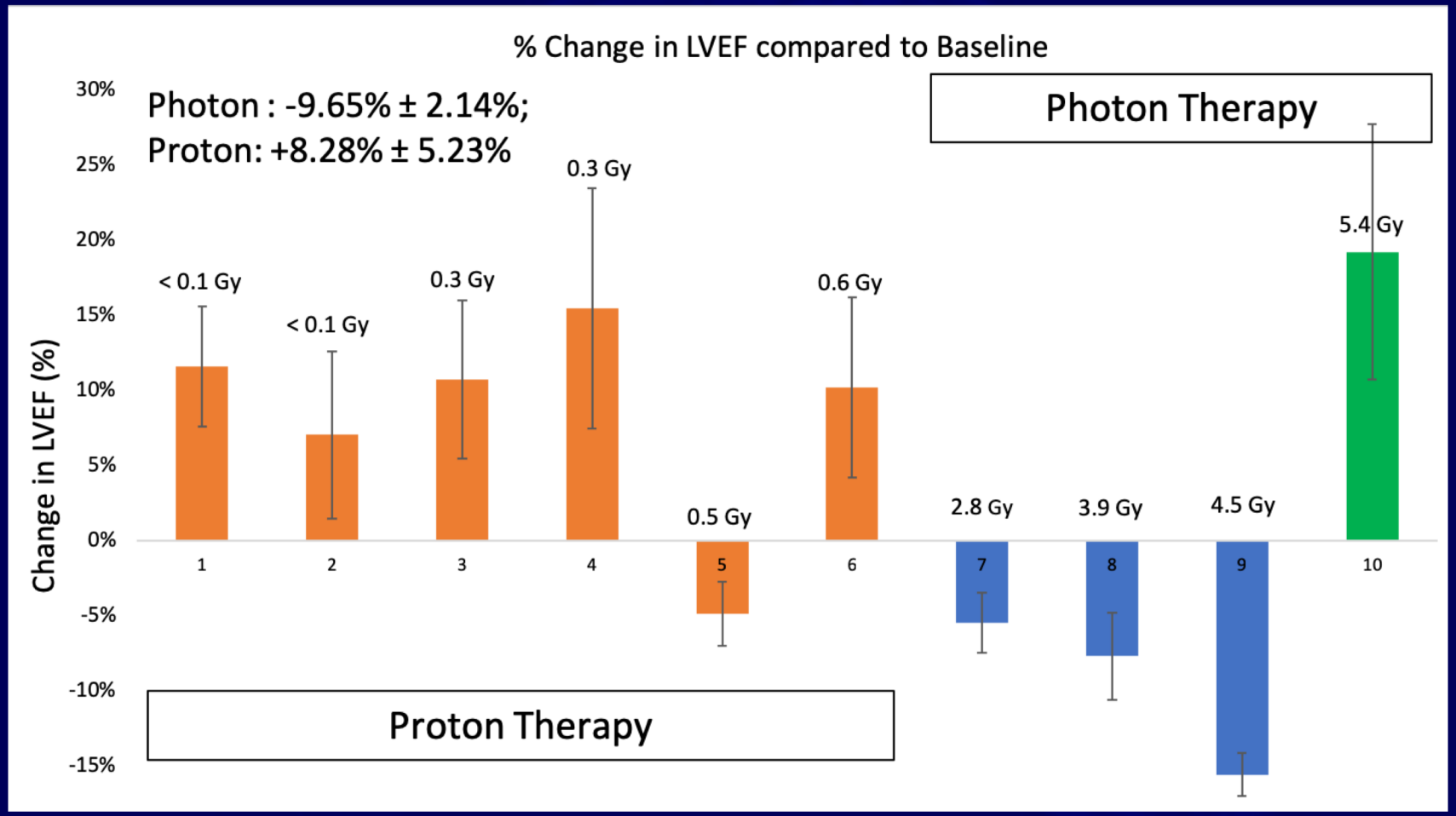
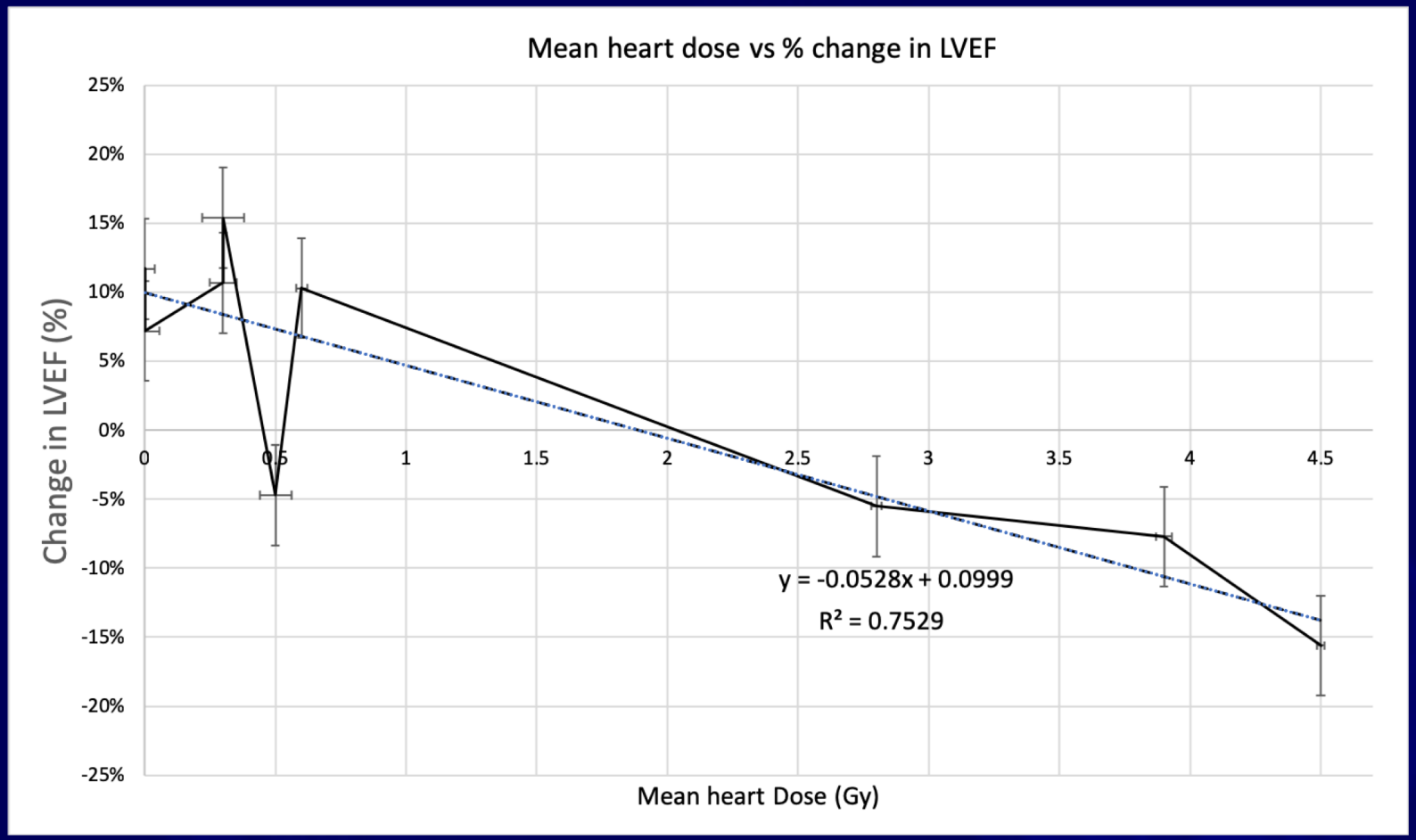
Change in LVEF versus treatment modality



ΔLVEF for Xray RT: -9.6 ± 2.1%
proton therapy: +8.3 ± 5.2% *p< 0.05

ΔLVEF vs Dose



LVEF decreased by 5.3% for each Gy increase in mean heart dose

ΔLVEF pre- Vs post-RT

Key points:

- No significant difference between the groups for age, BMI, smoking history, use of doxorubicin, baseline LVEF, scan interval, baseline diastolic volume.
- This is the first demonstration of the benefit of proton therapy in reducing heart toxicity.
- Changes are small enough that conventional LV volume methods could miss them.
- Improvement in some patients post-RT possibly due to chemotherapy-derived heart toxicity present at time of baseline MRI (before start of RT).

Regional Vs Global Effects

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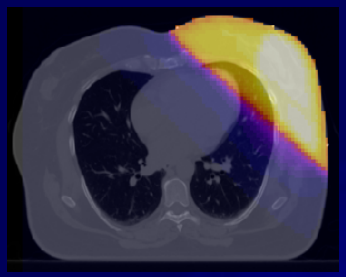
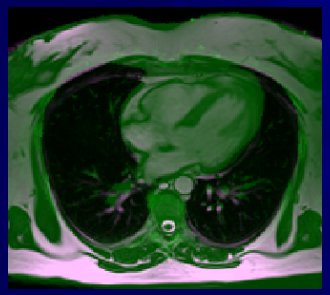
1: Heart RT dose is regional while LVEF is a global measure.

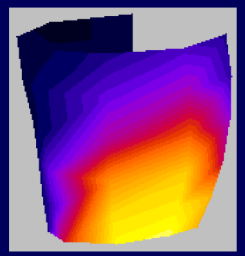
2. Register planning CT to heart MRI

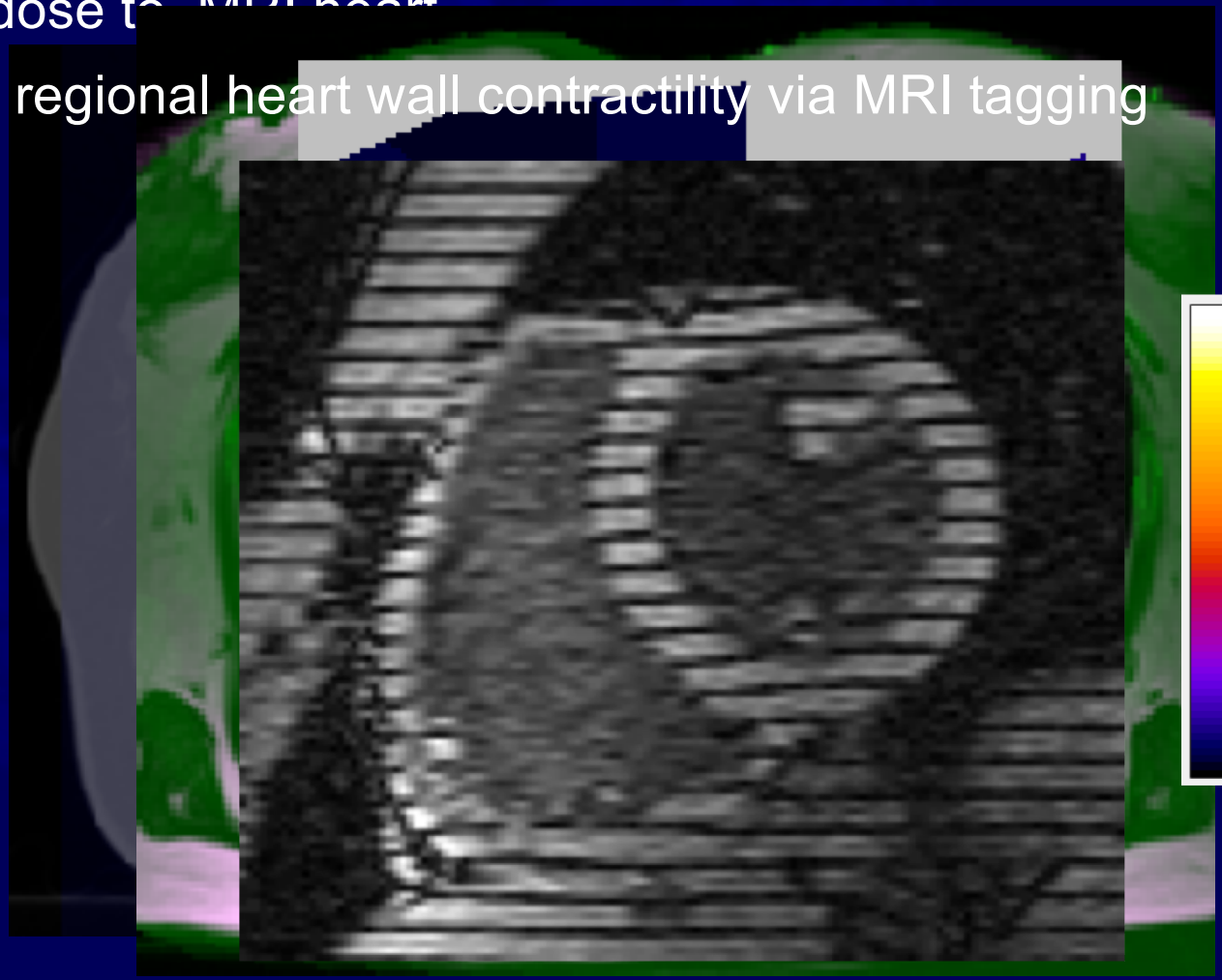
3. Map CT dose to MRI heart

4. Compute regional heart wall contractility via MRI tagging









MR Cardiac Tagging

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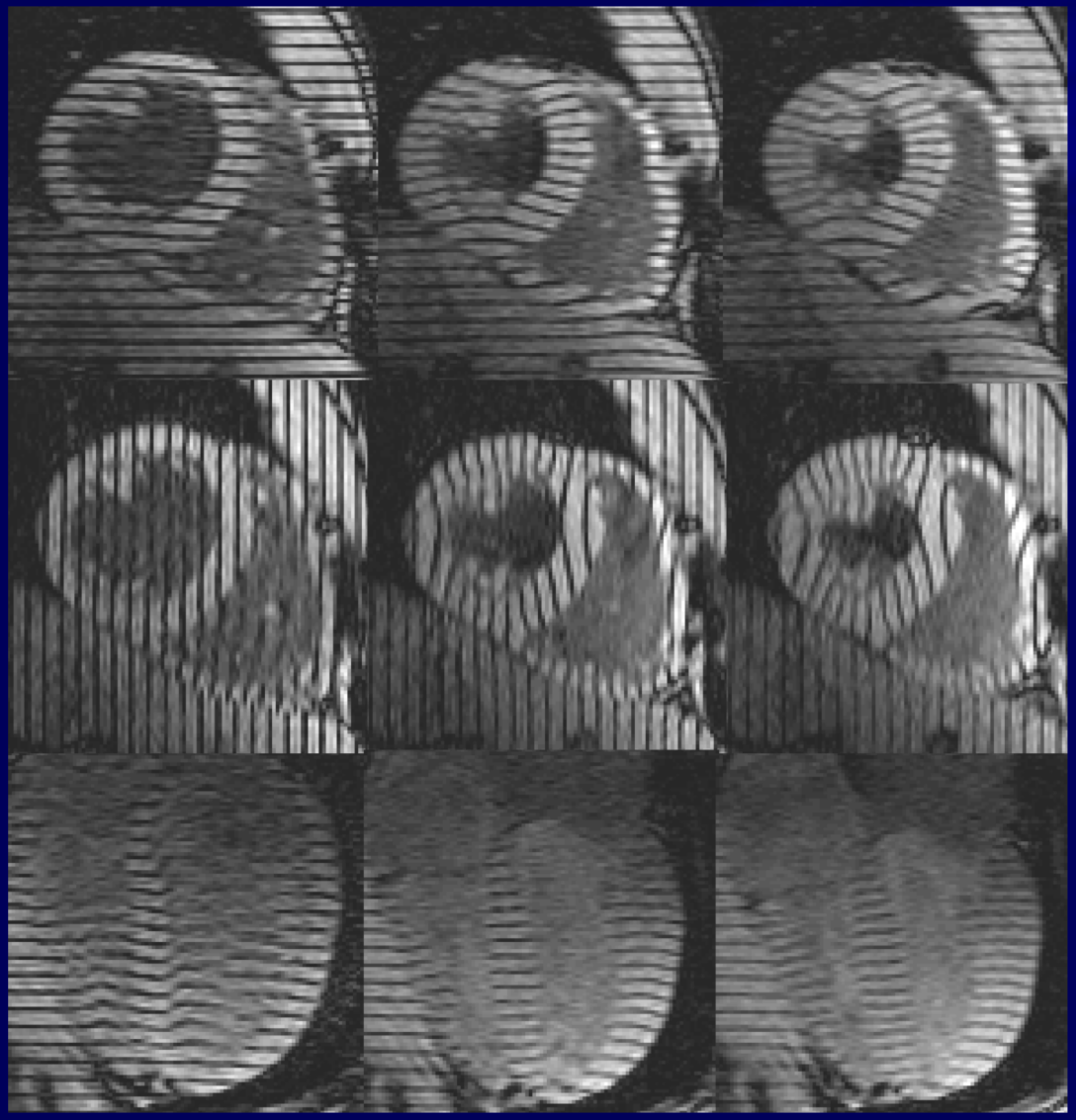
Tags

- regions of altered magnetization
- non-invasive
- persist ~600ms (T1 relaxation)

Parallel tagging/Acquisition

- optimal tag thickness and spacing
- partial K-space acquisition
- black-blood imaging
- breath-hold acquisition
- 20-30ms intervals
- 10-14 images during ejection

3D tagging



Vertical motion (dy)

Horizontal motion (dx)

Through-plane motion (dz)

Heart mechanical function

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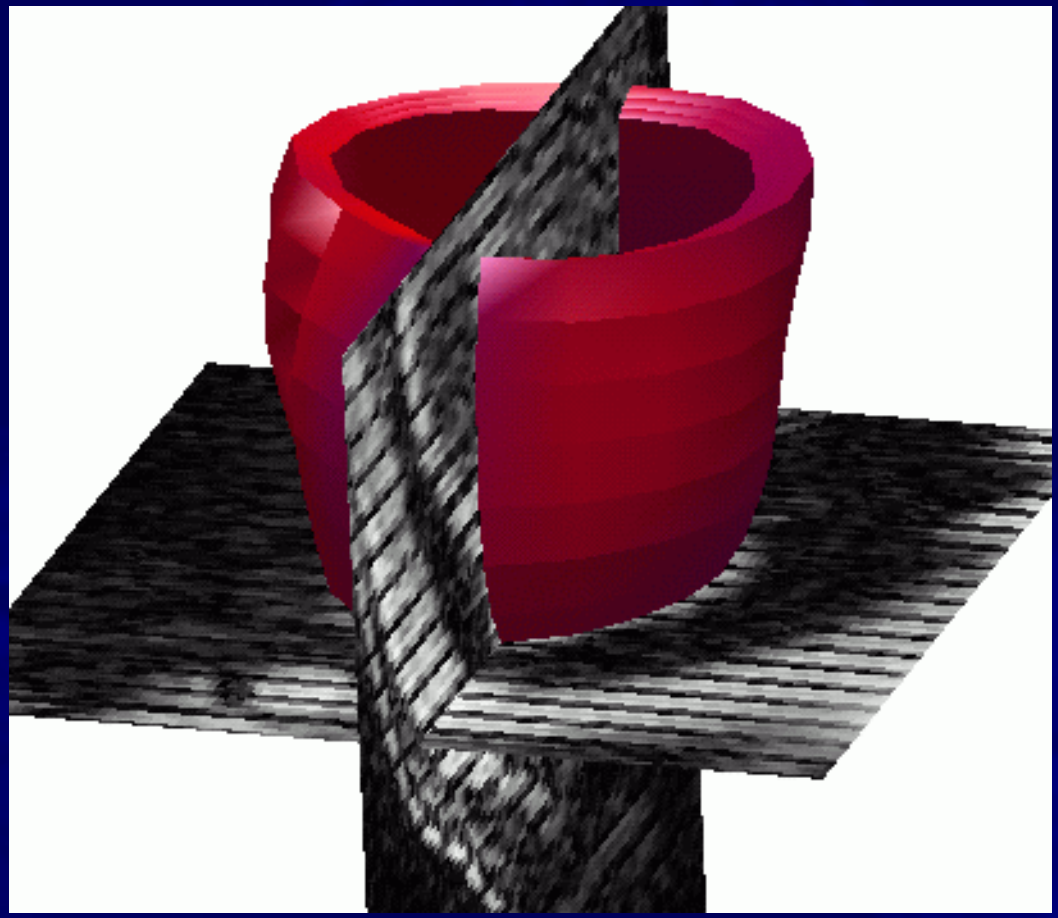
Goal: compute 3D strain throughout heart wall



Utility:

- assessing long-term cardiac toxicity: cardiomyopathy
- Acute radiation in-field damage: regional wall dysfunction

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Dose vs strains

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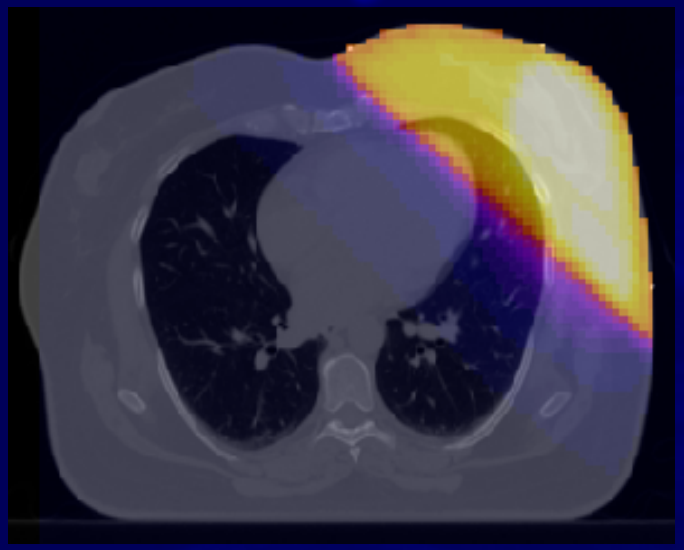
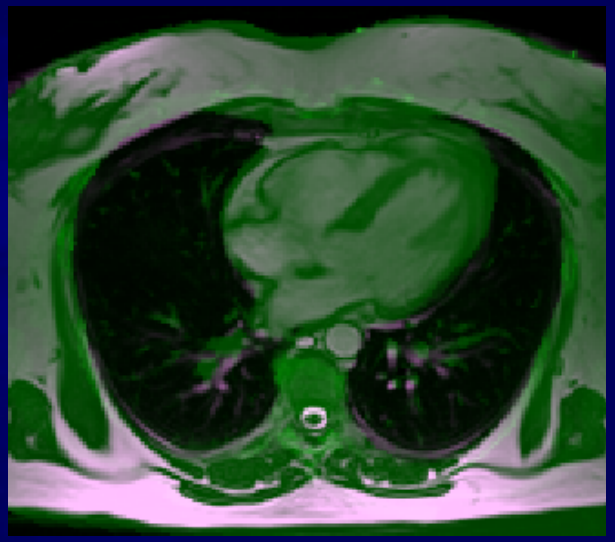
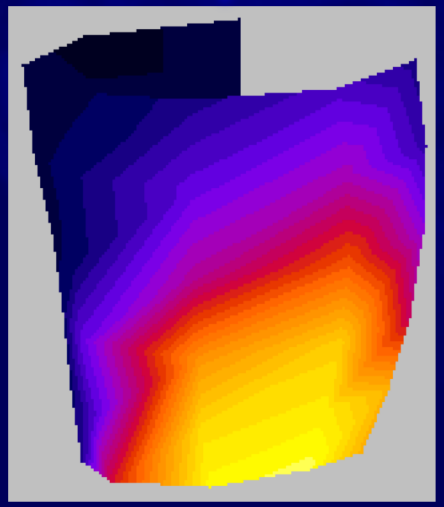
Planning CT



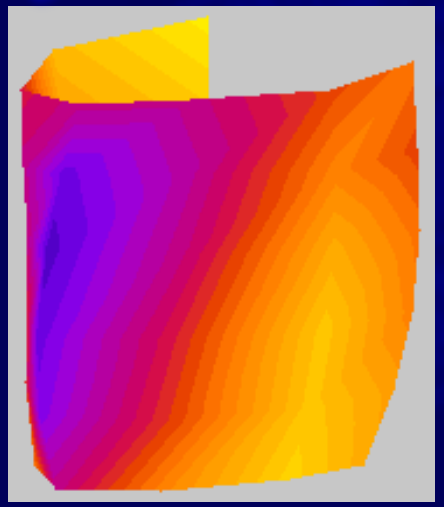
CT to MR registration



Dose warped to LV



Change in circumferential strain



Future Funding

NIH NCI RO1 PAR-19-112
Improving Outcomes in Cancer Treatment-Related Cardiotoxicity

Title: Prospective Study of Early Markers of Radiation-Induced Cardiac Injury in Breast Cancer Patients

PIs: O'Dell, Bradley (UF, UFPTI); Ambrosini, Milano (URMC)

Aim 1: Repeated MRI-LVEF and liquid biopsies to document onset and progression of cardiac toxicity.

Aim 2: Compare incidence and severity of toxicity: PT vs. IMRT/CRT

Aim 3: NTCP-model radiation dose, blood-borne markers, and patient-specific factors (chemo, smoking, etc.) to predict risk for major cardiac events.

Aim 4: Exploratory: Correlate regional dose to changes in regional myocardial strain and perfusion

5 years, 60 patients, 300 scans and blood draws, ~$2.5M

Resubmission deadline Nov 5, 2019

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UF	URMC
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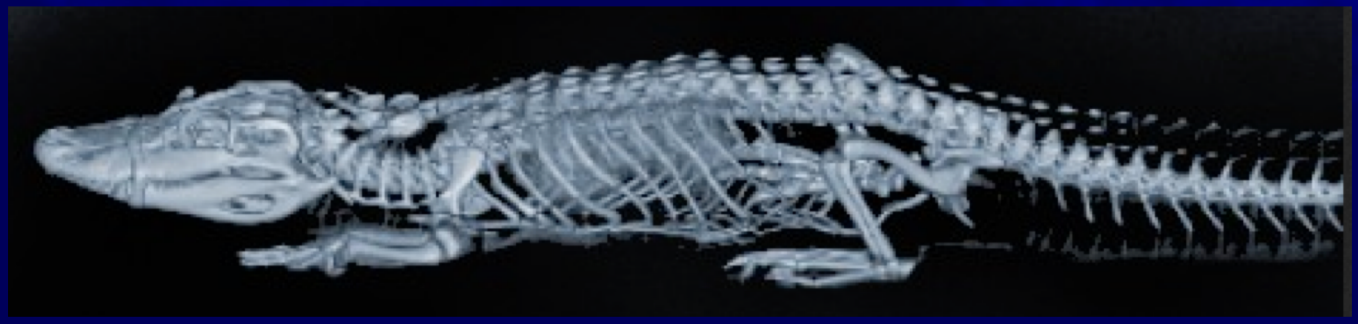

Questions/comments?

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Circumferential Strain

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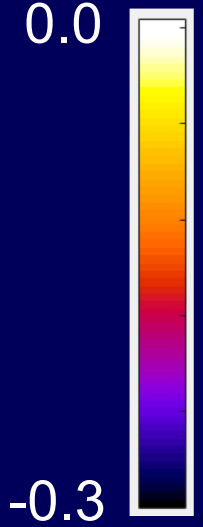
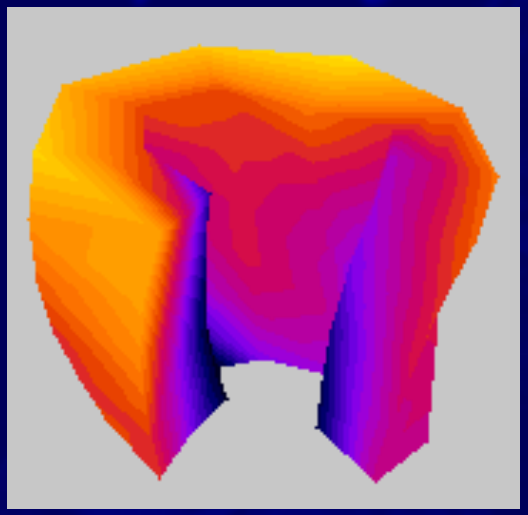
CRT patient

Circumferential strain at full contraction (range 0.0 to -0.3)

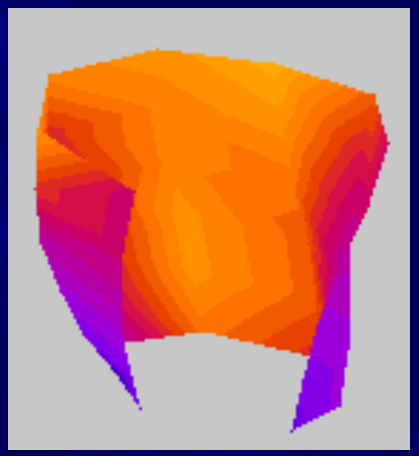
All layers through wall

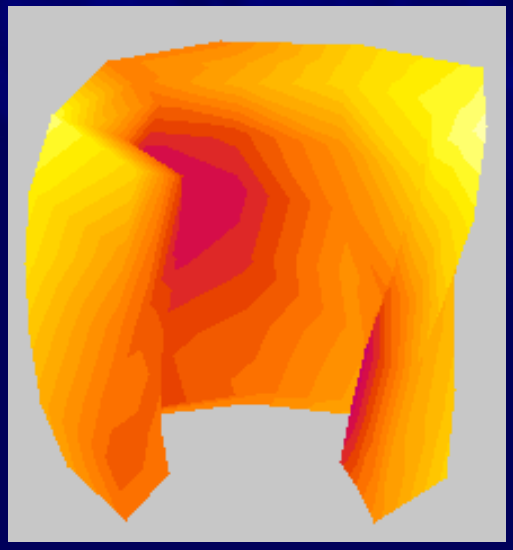
mid-wall only





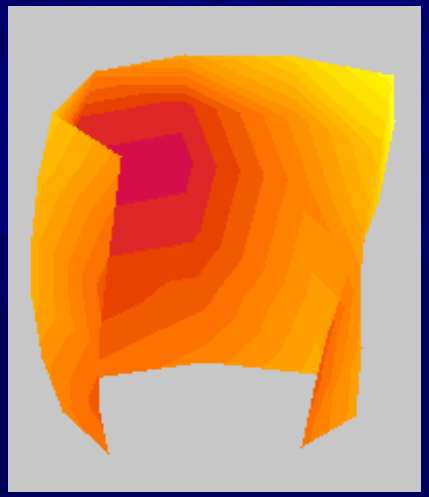
Pre-RT





12-months post-RT

Decreased Ecc
Increased LV Volume
Decreased LVEF



Breast Cancer Patients

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Patient #12: Mid-wall Circumferential Strain Multi-Plots

Blue = pre-treatment, red = post-RT