

The Science of Regenerative Medicine



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What is the difference between Sports Medicine and Radiation Oncology?

Sports Medicine

- Faster Cars

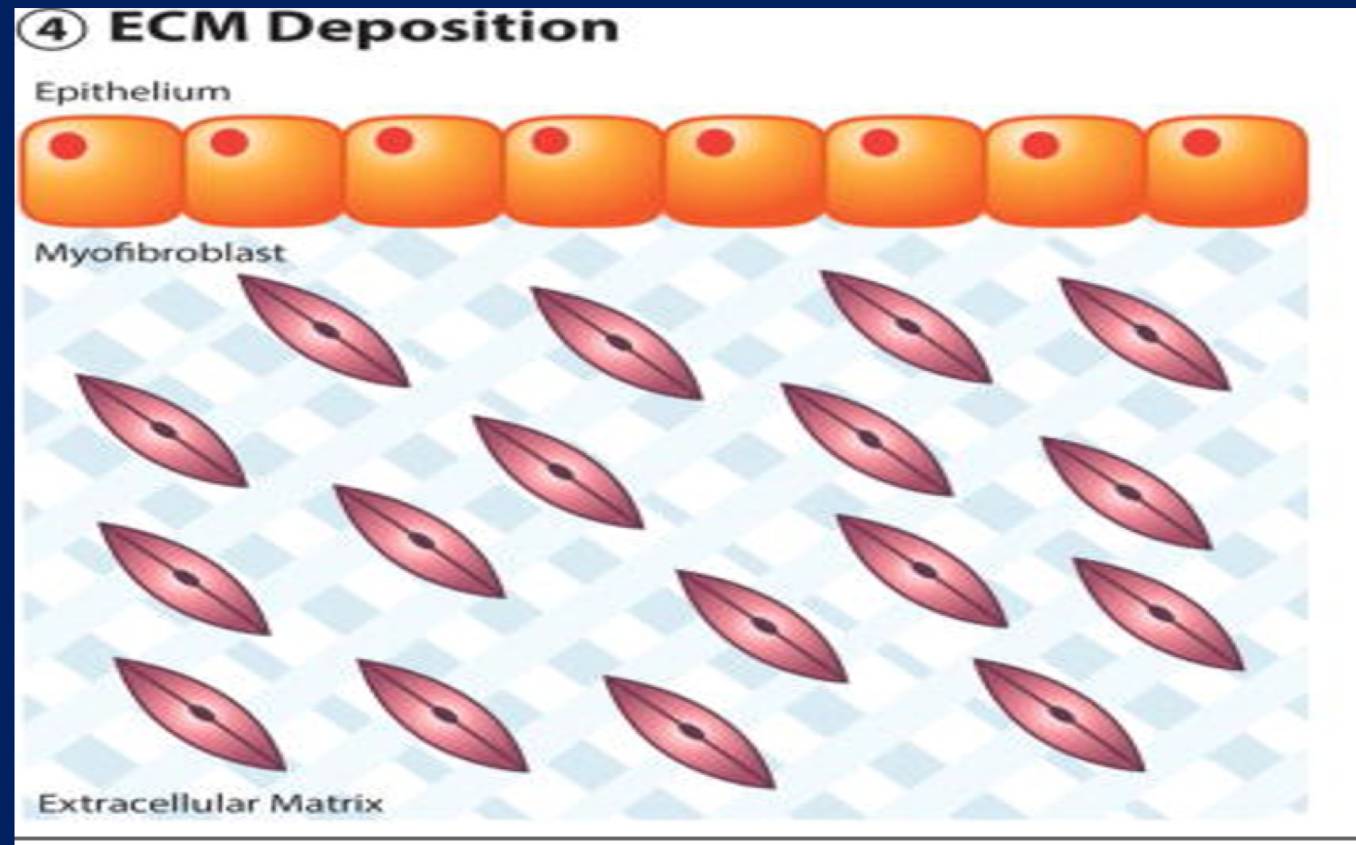


Radiation Oncology

- Bigger Machines



what we have in common could improve all
of our patients' lives



Normal Tissue Fibrosis from Treatment:

Sports Medicine

- Surgery
- Injury

Cancer Therapy

- Surgery
- Radiation
- Surgery + Radiation
- Surgery + Chemotherapy + Radiation

All can result in:

Misguided , overstimulated wound response resulting in collagen deposition, and scarring

Fibrosis leads to poor outcomes including loss of function, pain, and/or decrease in QOL

Radiation Therapy for Cancer Saves Lives!



Saves limbs
Alternative to Surgery
Saves Lives

Saves breasts
Saves voices
Cures Cancer

However, the long term side-effects of radiation treatments can impact a patient's quality of life with progressive irreversible changes resulting from radiation-induced fibrosis

Defining Radiation-Induced Fibrosis:

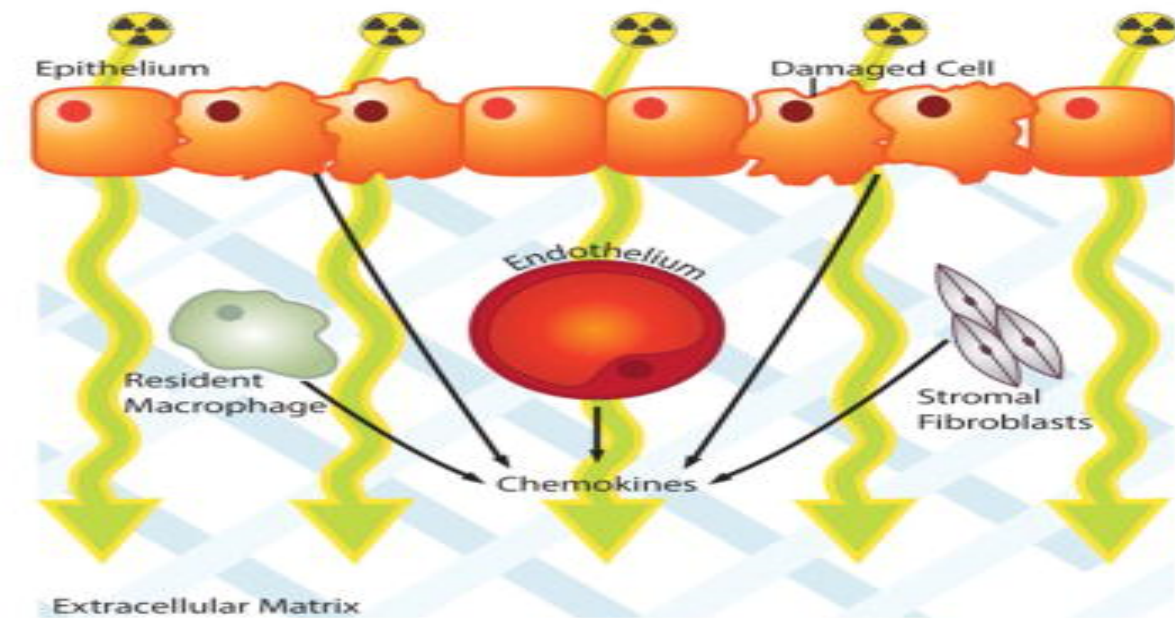
- Site specific: inside the radiation field
- Dose dependent: higher doses cause more fibrosis
- Time to onset is 3-12 months after radiation treatment
- Causes pain, loss of function, and a decrease in quality of life

Many Clinical Examples of Radiation-Induced Fibrosis

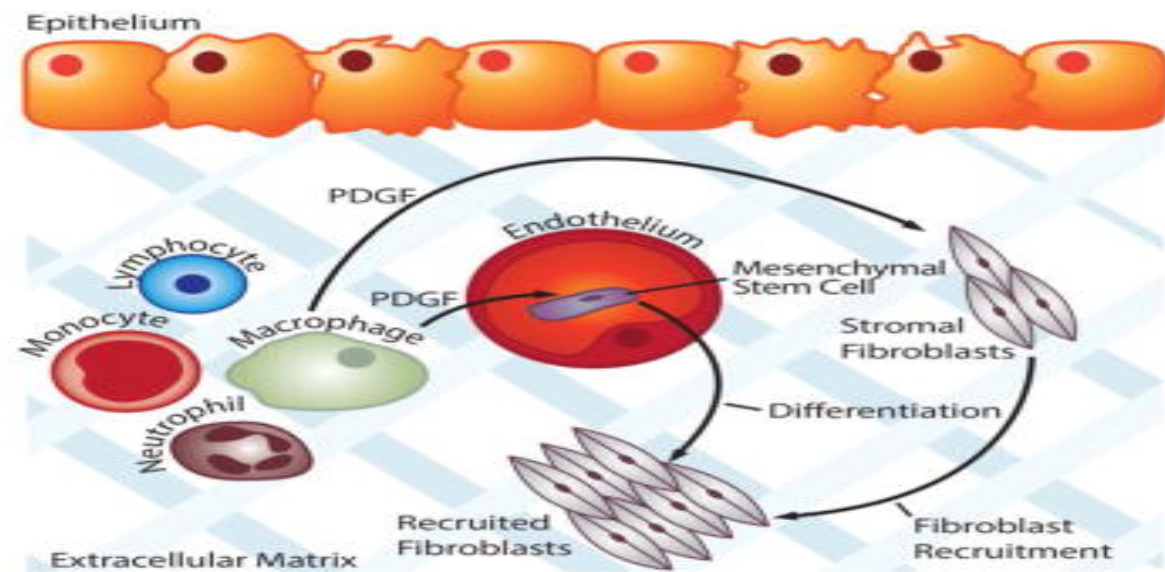
because it occurs in every site we treat:

- Lung cancer.....difficulty breathing, heart damage
- Breast Cancer.....breast shrinkage, lung scarring, heart damage
- Prostate Cancer.....loss of sexual functioning, incontinence
- Head and Neck Cancer.....difficulty swallowing, decreased saliva, muscle stiff
- Brain Tumors.....loss of intellect and memory
- GYN Cancer.....vaginal stenosis, urinary leaking
- Sarcomas.....muscle stiffening, lymphedema
- Esophageal Cancer.....strictures, difficulty swallowing
- Anal Cancer.....Pain with bowel movements

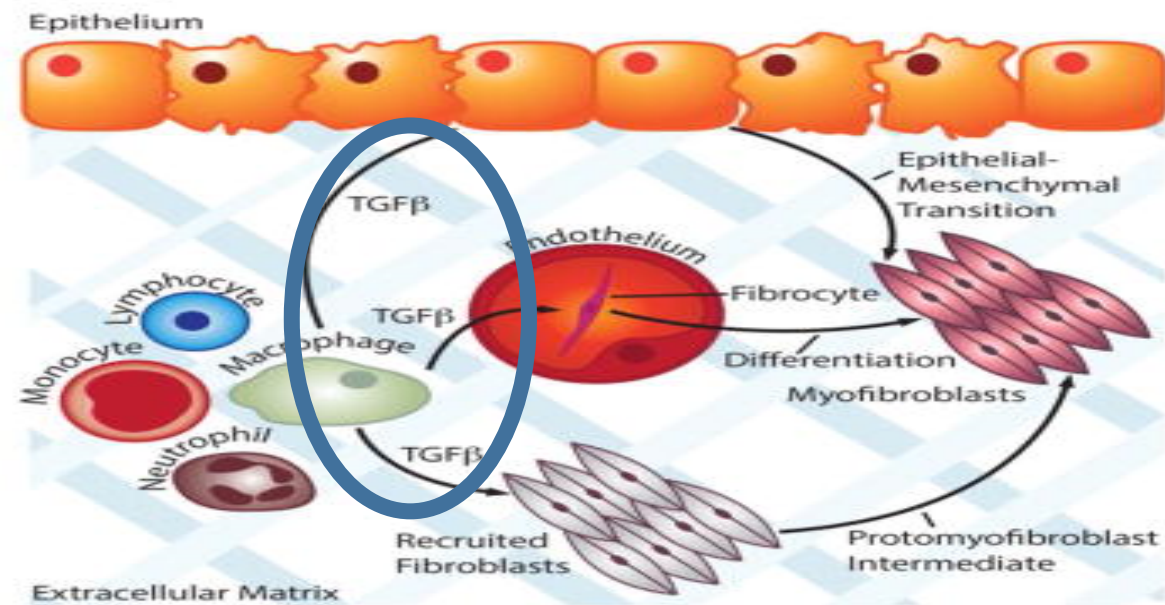
① Initial Injury



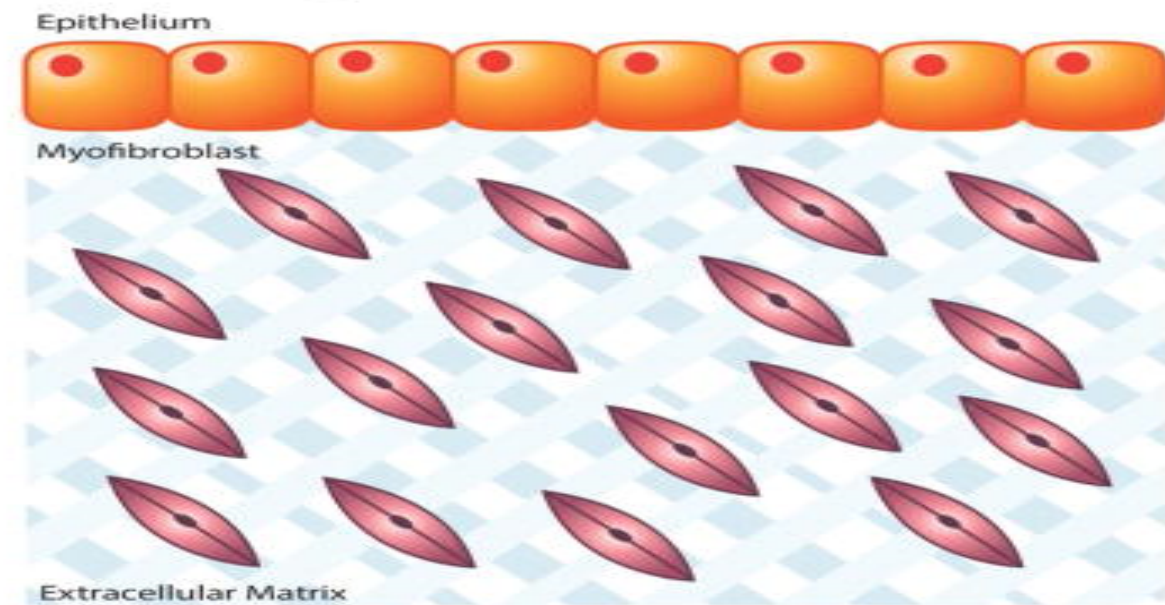
② Inflammation & Fibroblast Recruitment



③ Myofibroblast Production

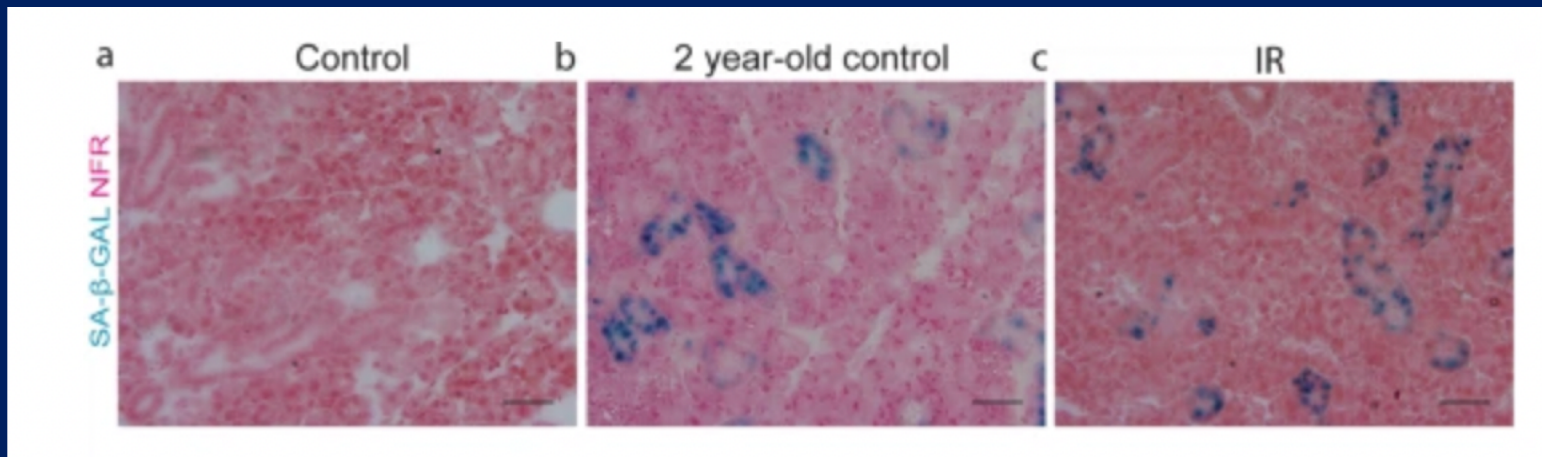


④ ECM Deposition



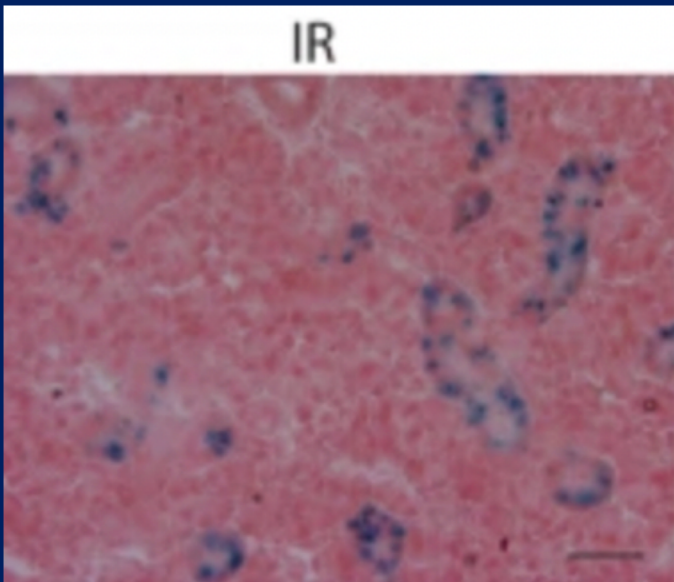
Stress-induced cellular senescence occurs after DNA damage with radiation

A mixture of pro-inflammatory molecules secreted by senescent cells includes senescence-associated secretory phenotype (SASP) molecules, one of which is TGF- β 1.

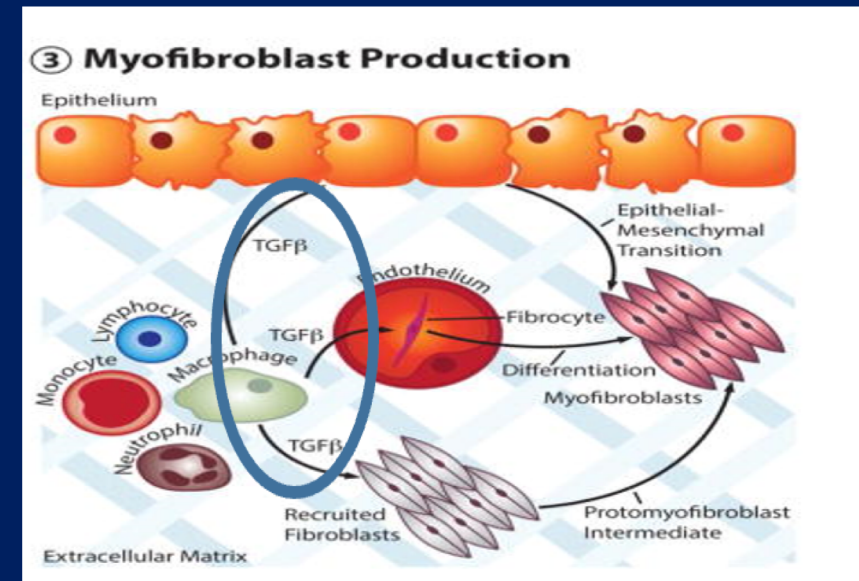


Mechanisms of Radiation-Induced Fibrosis:

Cellular senescence

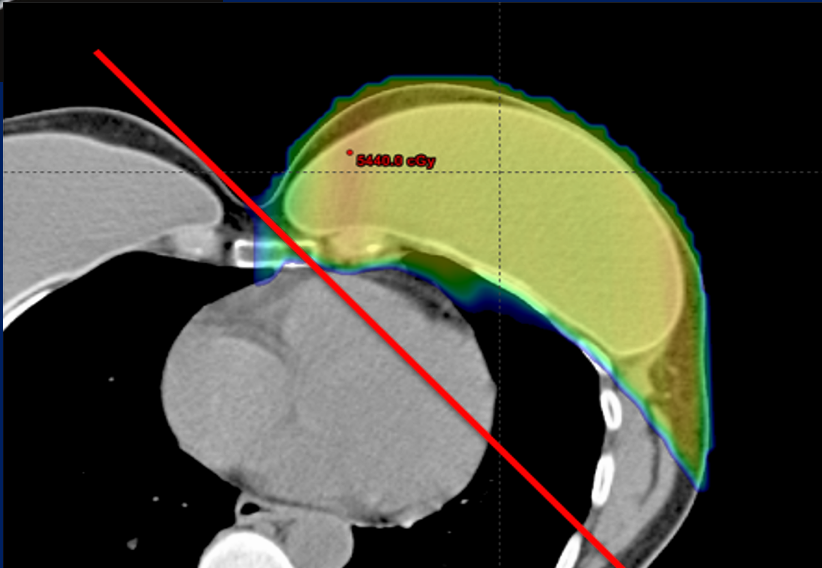
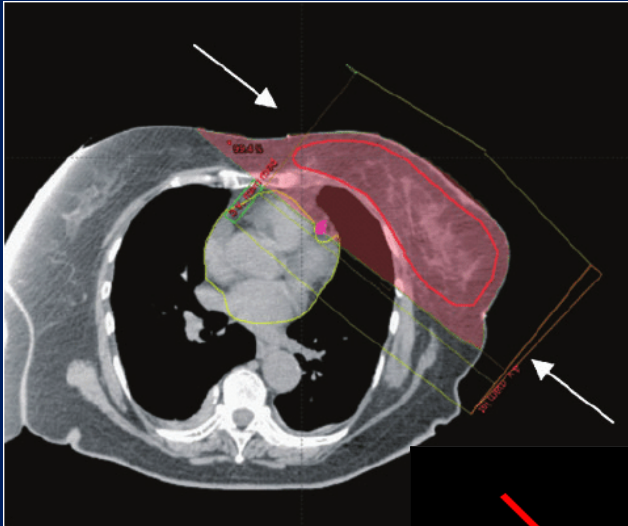


Elevated TGF- β 1



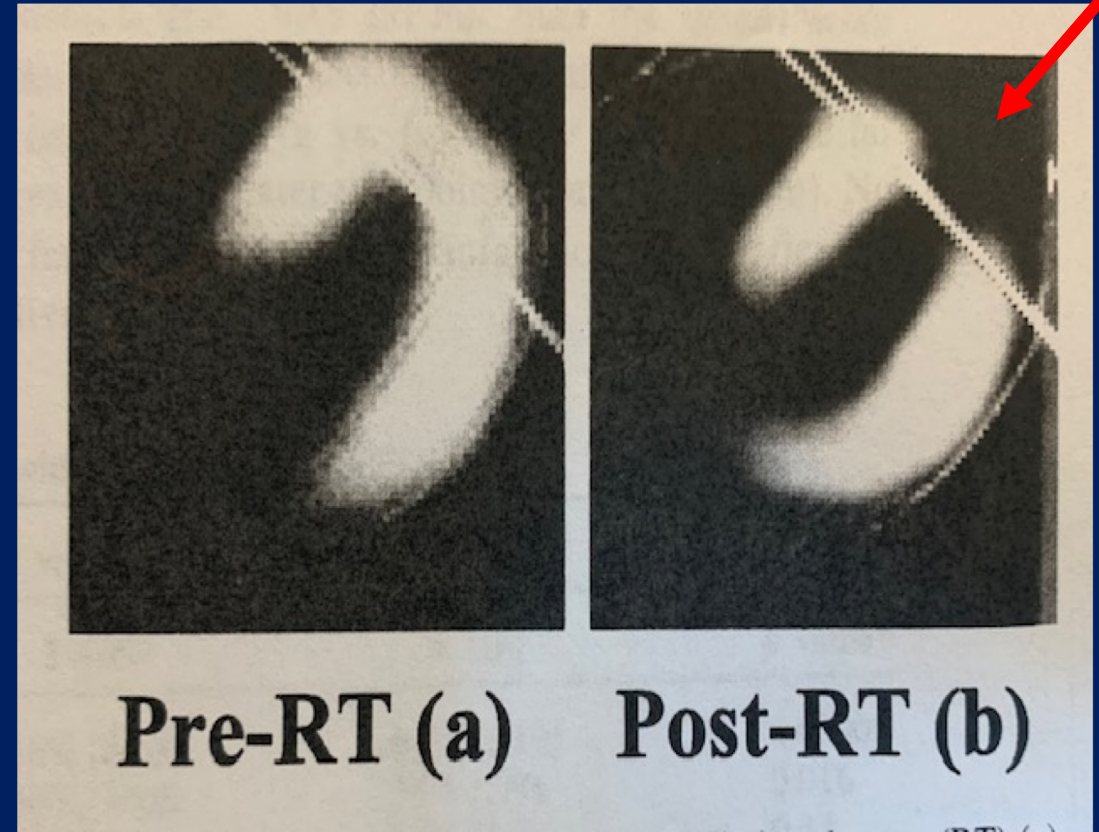
Human Example:

Radiation-Induced Heart Disease in Left sided Breast Cancer



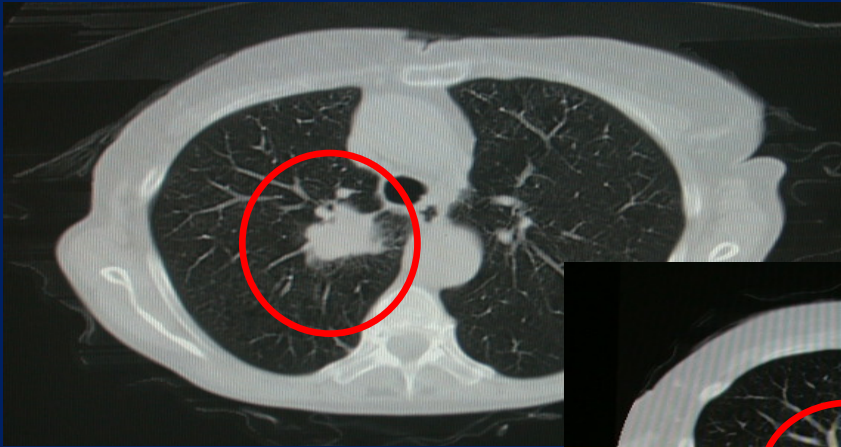
Breast Radiation tangent fields

Non perfused irradiated muscle



Cardiac SPECT perfusion images

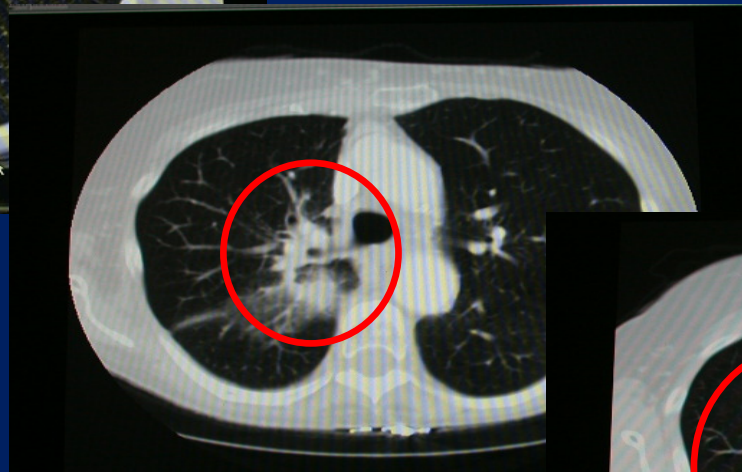
Radiation-Induced Fibrosis in Lung Cancer



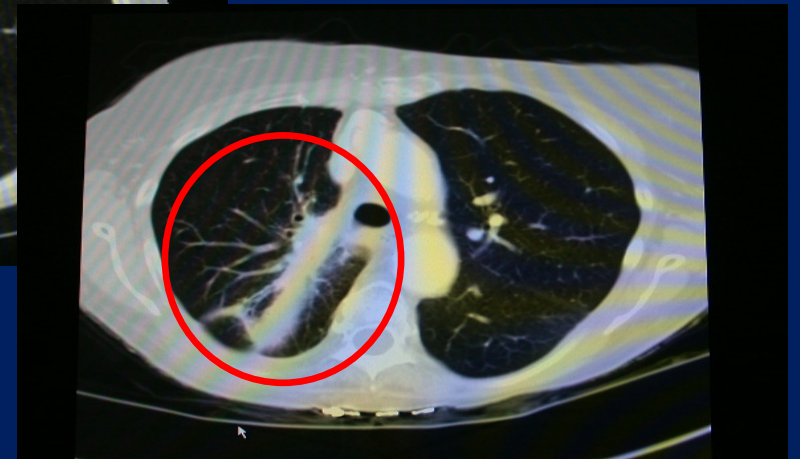
Pre-Rx



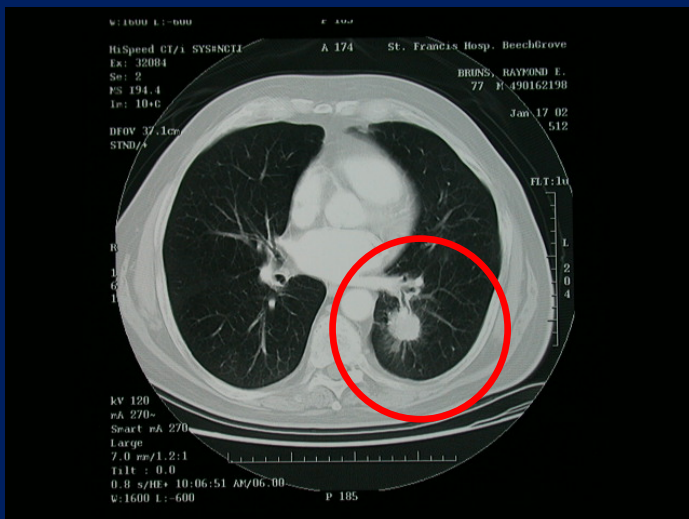
3 mo.



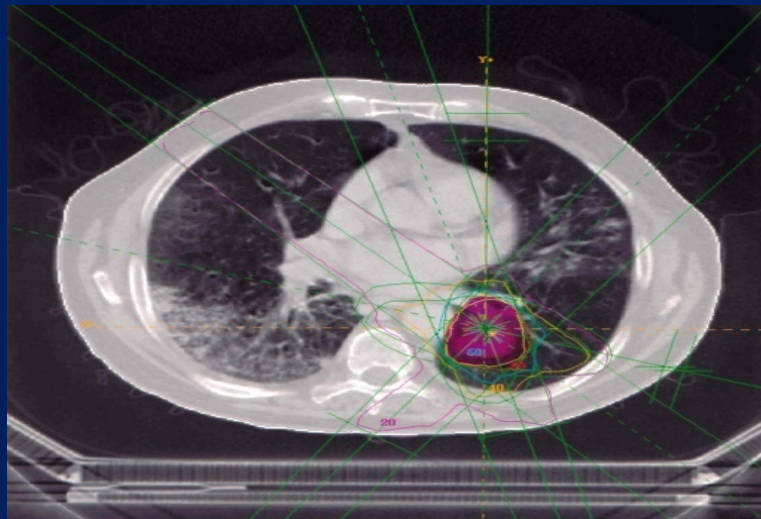
9 mo.



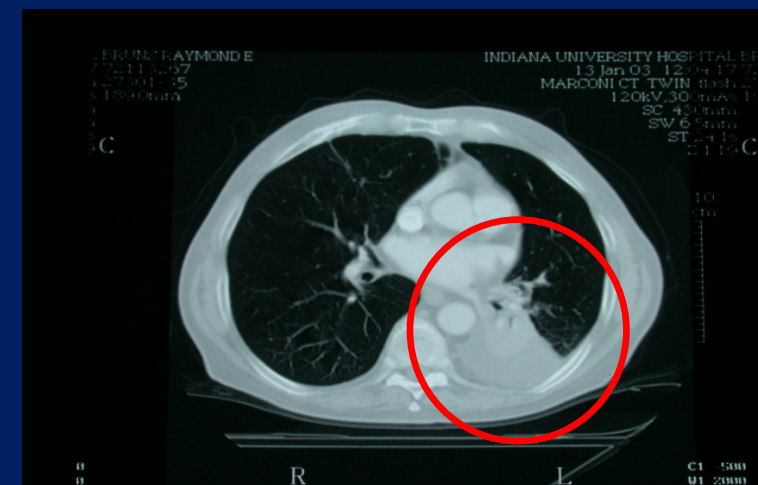
18 mo.



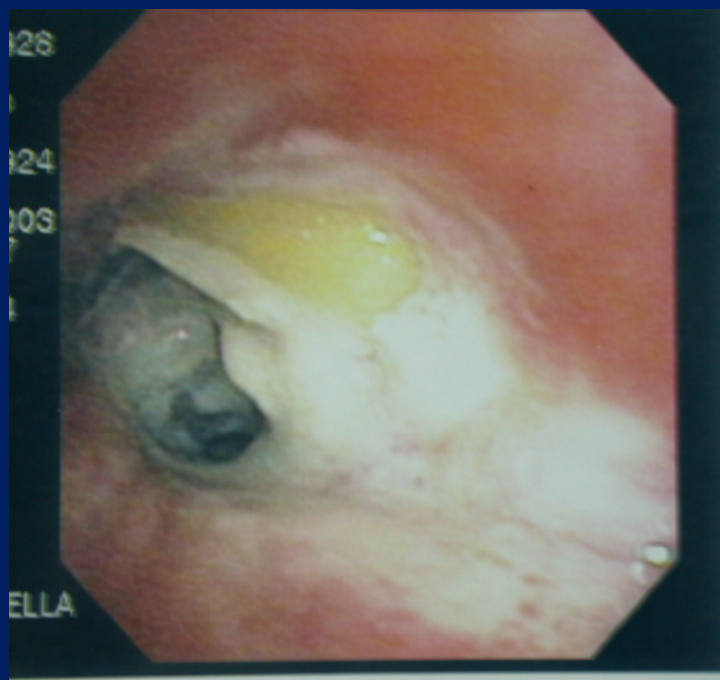
Pre-treatment



Treatment planning



One year post treatment



Post treatment bronchoscopy

**Wedge-like collapse
of segmental bronchus**

**No evidence of tumor
recurrence on PET**

**No tumor cells on bronchial
biopsy or brushings**

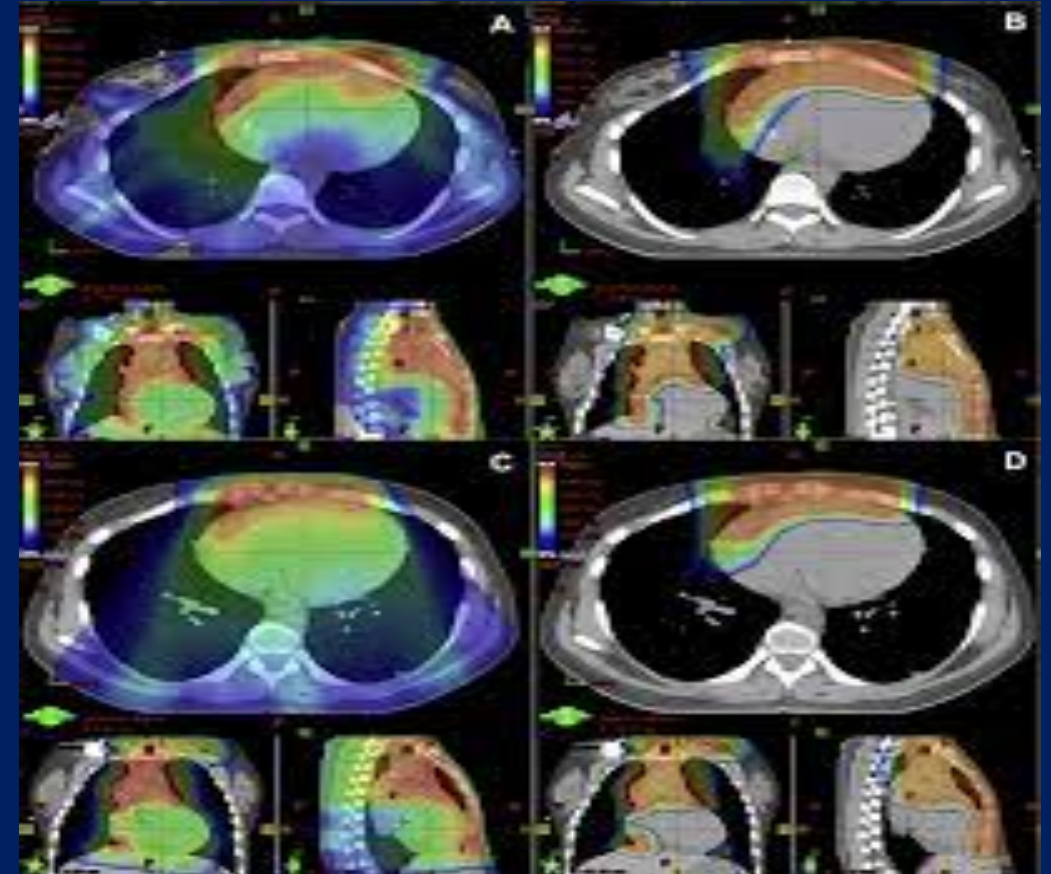
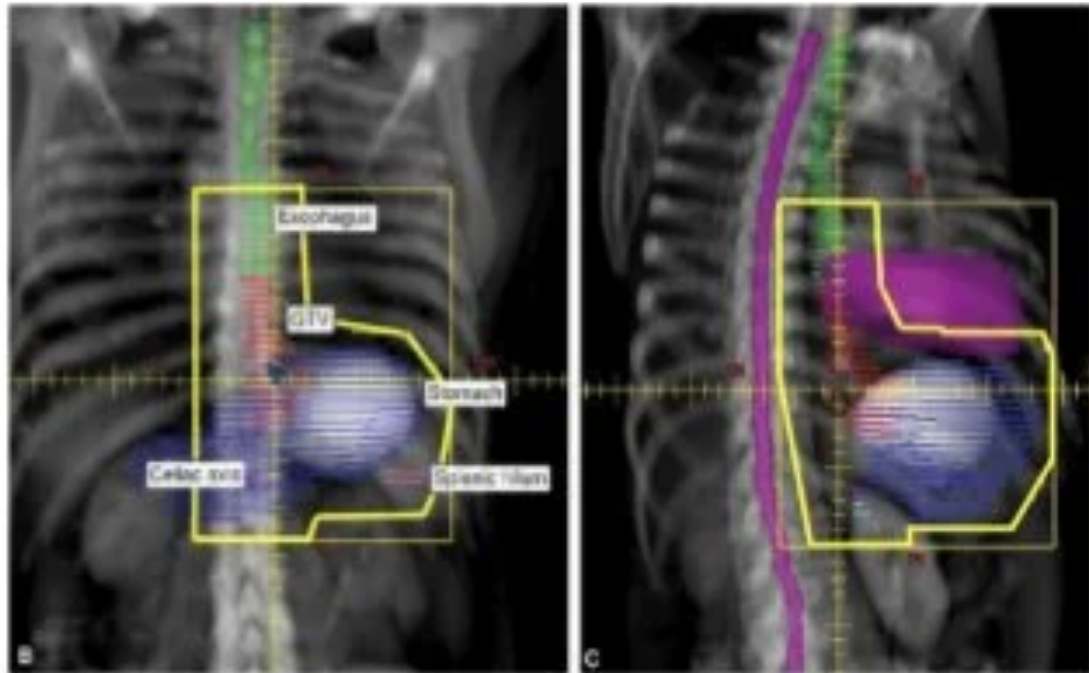
Radiation-Induced Fibrosis Causes Heart Disease

Cancer sites getting radiation in close proximity to the heart:

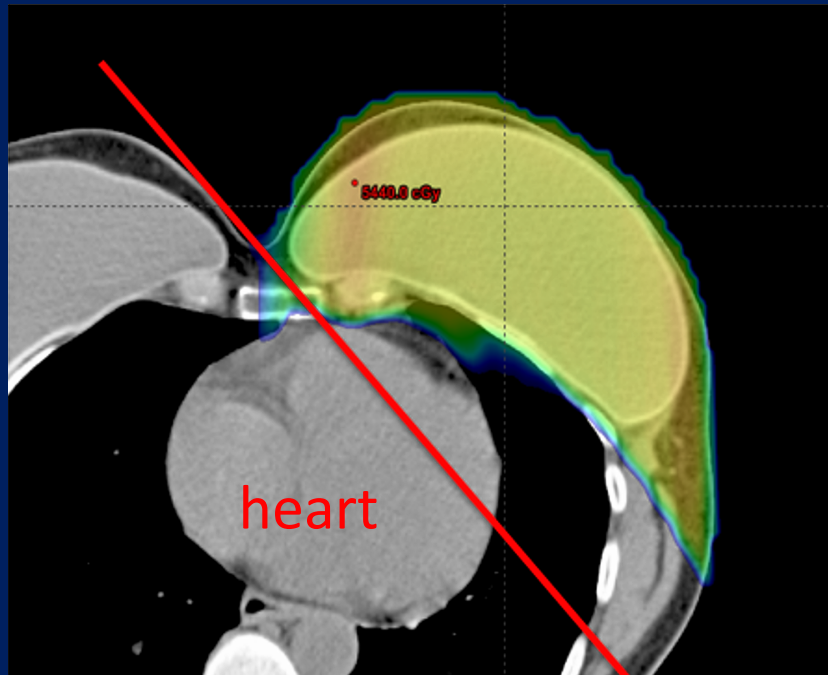
Esophagus

Lymphoma

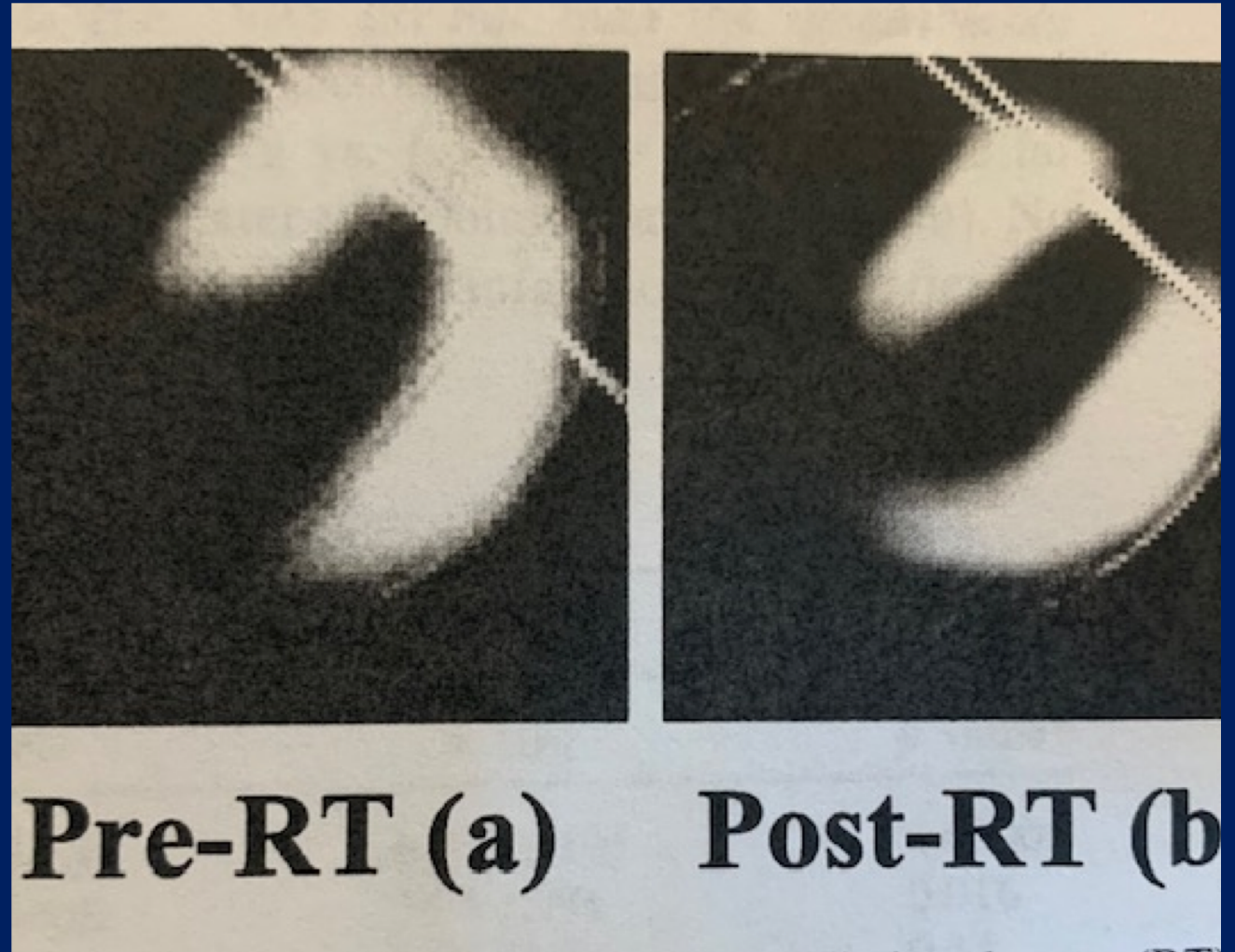
Typical Radiation Field for Lower Esophagus



Radiation-induced
Fibrosis leads to a
decrease in blood supply



Cardiac SPECT perfusion images

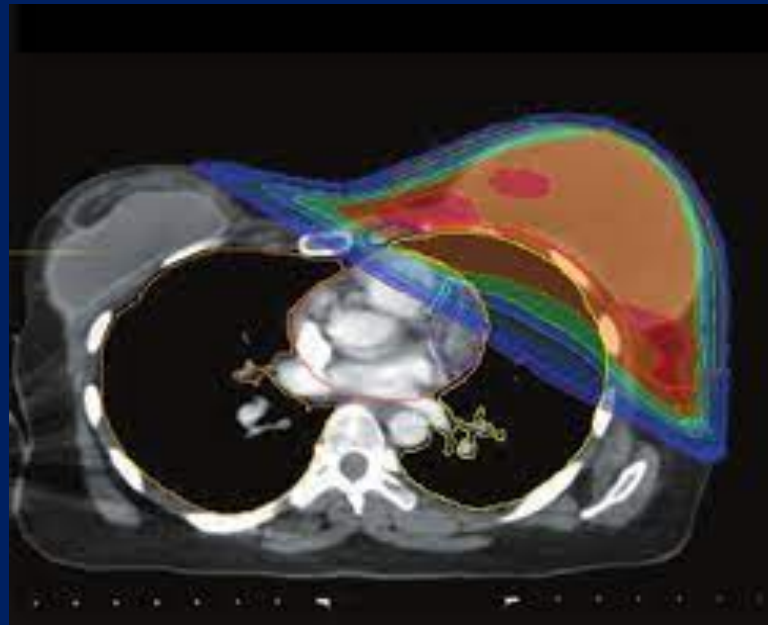


Breast Cancer and potential outcomes:

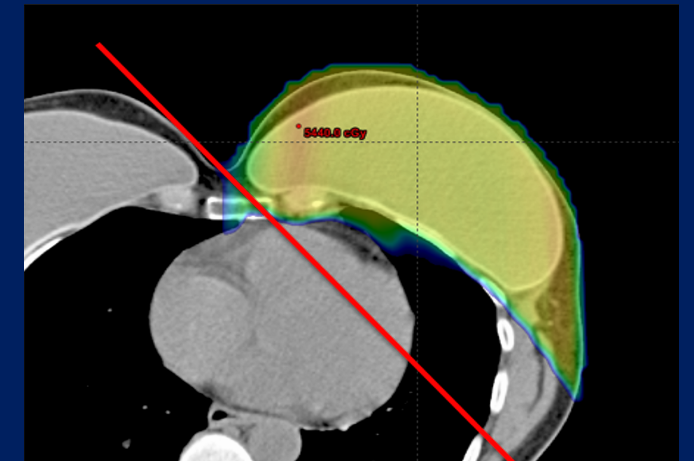
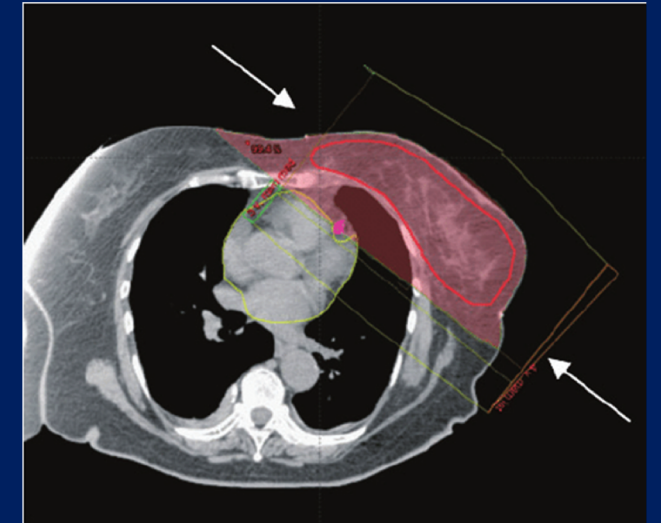
Typical treatment is : surgery + chemotherapy + radiation

Fibrosis leads to:

- skin thickening
- breast tissushrinkage
- heart damage
- lung scarring



Typical Radiation field



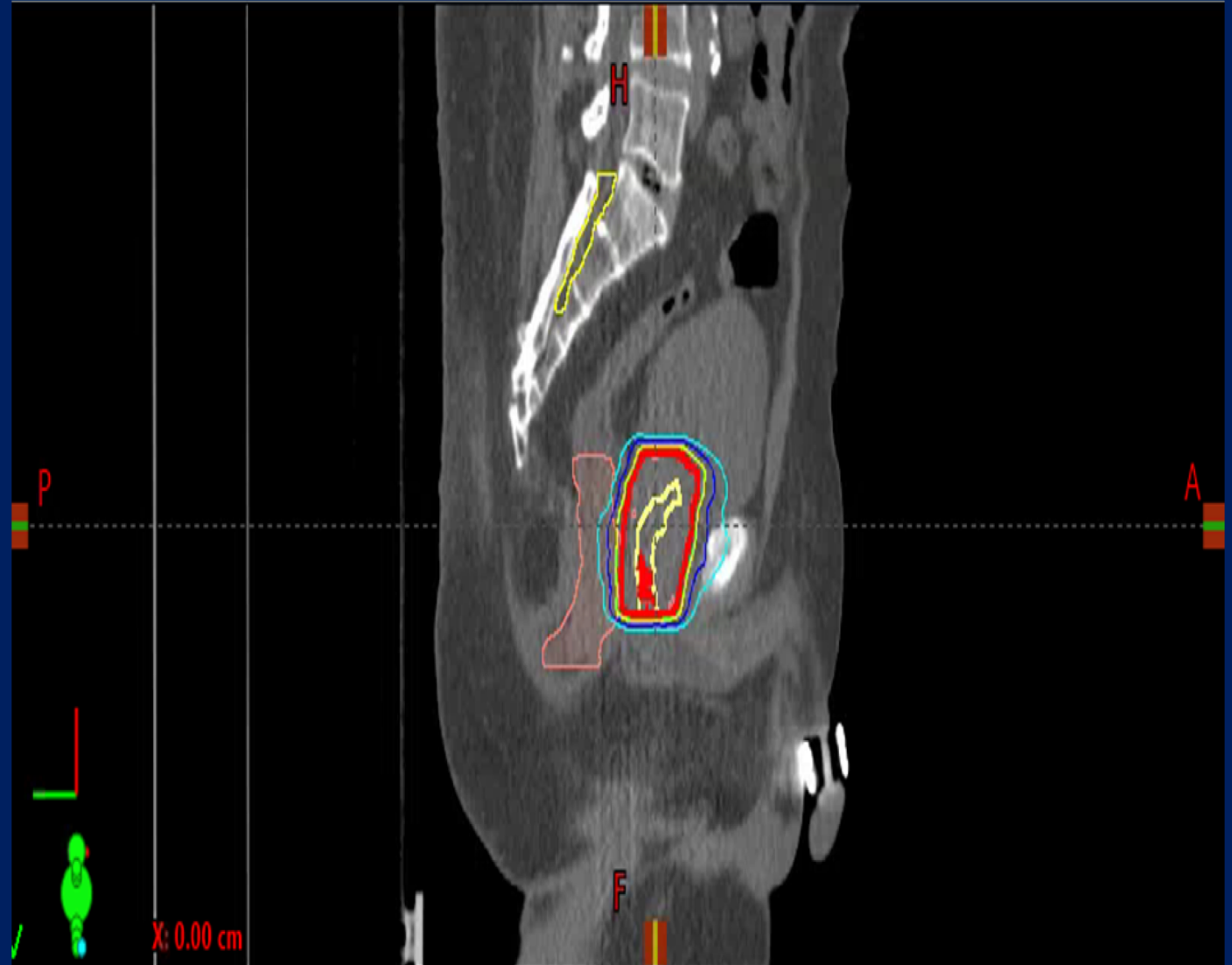
Prostate Cancer

Fibrosis leads to:

Urethral Strictures

Urinary Incontinence

Sexual Dysfunction



What if we could Save lives and Not cause Radiation-Induced Fibrosis?

difficulty breathing

breast shrinkage, lung scarring

loss of sexual functioning, incontinence

difficulty swallowing, neck muscle stiffening

loss of intellect and memory

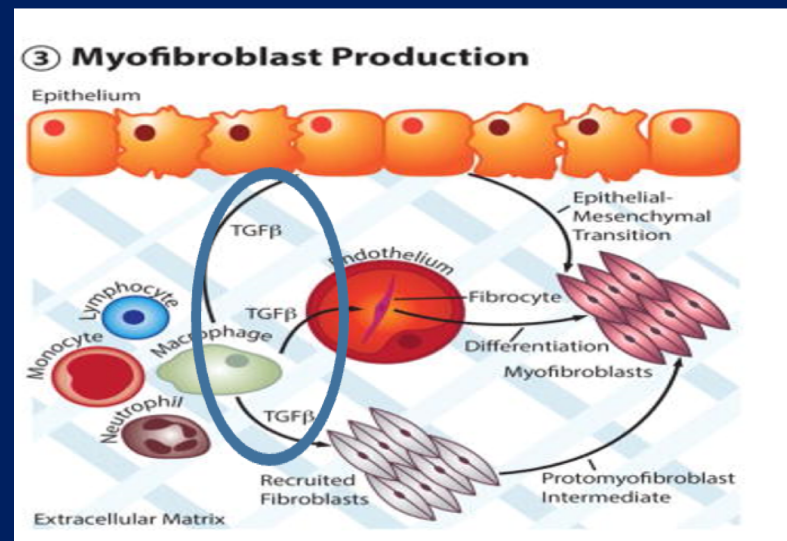
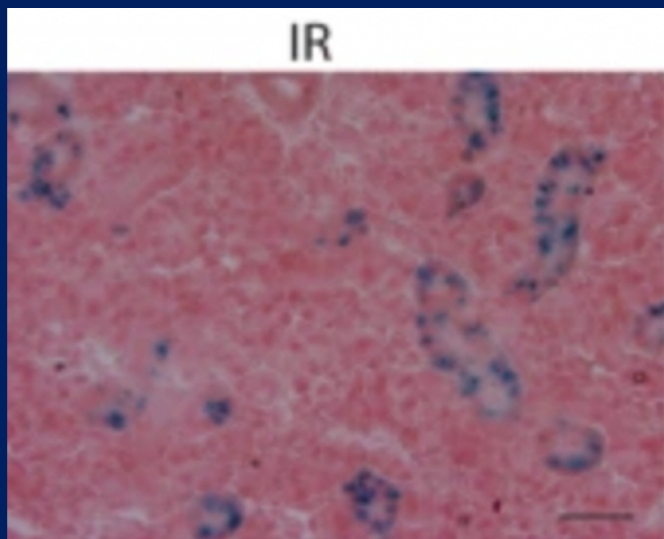
vaginal stenosis, urinary leaking

muscle stiffening, lymphedema

strictures, difficulty swallowing

There are No Successful Treatments for Radiation-Induced Fibrosis

- Our strategy is directed at drivers of the development of Fibrosis:
 TGF-B1 and Senescent Cell cytokine production
- Draws from knowledge of how fibrosis forms, **based on 20 years of work from Huard lab**
- It assumes a similar approach to the fibrotic process as that which occurs in orthopaedic and sports medicine injuries thus **Building on the SPRI approach**



Implications for therapy:

Pre clinical studies aimed to mitigate radiation induced fibrosis in a mouse model by inhibiting TGF-B

TGF-B and its associated signaling molecules have been examined as therapeutic agents

Molecule	Antagonism	Site	Ref
LY2109761	TGF-B1	Lung	Flechsig (2012)
Halofuginone	TGF-B2	Breast	Xavier (2004)
Losartan	TGF-B1	heart	Kovacs (2021)
SB-505124	TGF-B1	muscle	Gans (2020)

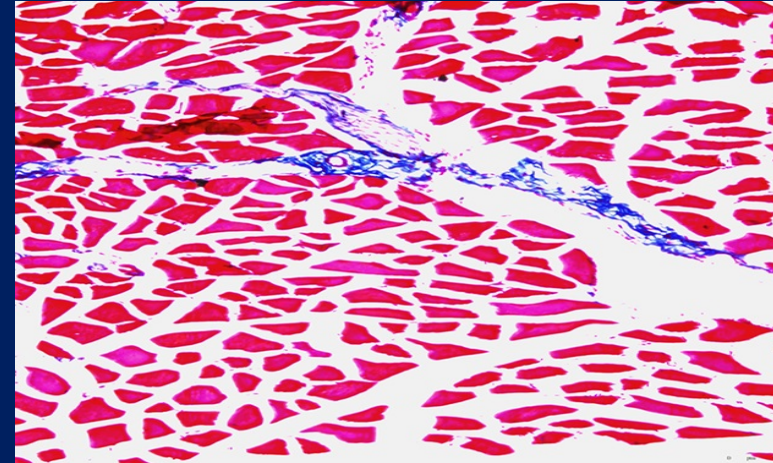
Administration of **TGF-B Inhibitor** Mitigates Radiation-Induced Fibrosis in a Mouse Model

50 Gy of radiation to the hind limb

Slides show muscle of a mouse

9 months later

50 Gy only



Red indicates muscle, **blue indicates fibrosis**

50 Gy + TGF-B inhibitor
Given IP, daily for 8 weeks



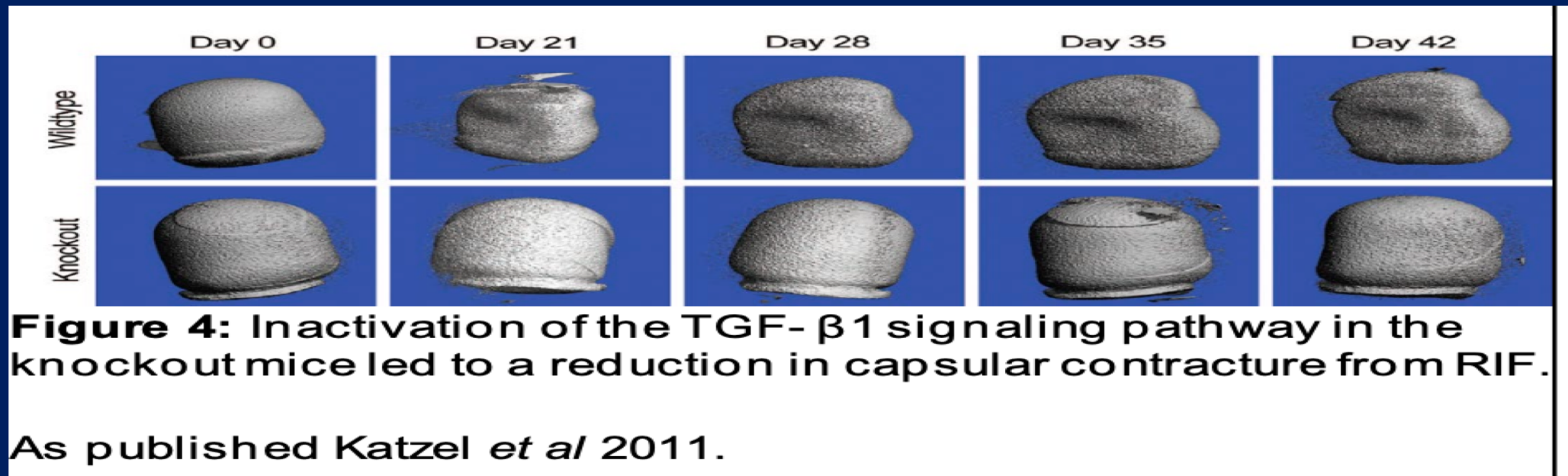
The Impact of SMAD3 loss of function on TGF-B signaling

48 mice :

wild type vs Smad3 knockout (loss of TGF-B function)

Implanted with silicone gel implants

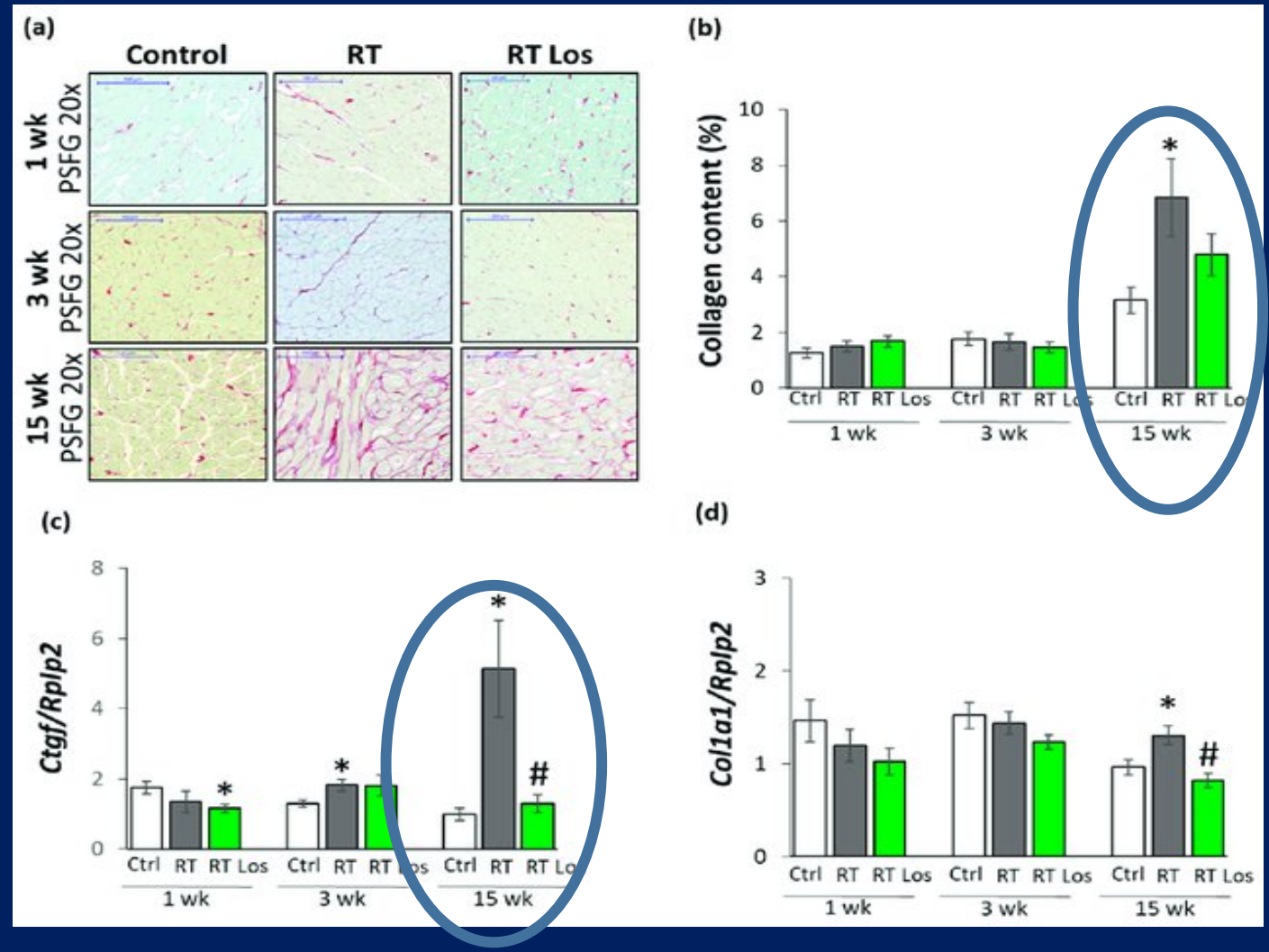
Irradiated implants 10 Gy



Investigation of the Antifibrotic Effects of **Losartan** in a Rat Model of Radiation Induced Heart Disease

At 15 weeks:

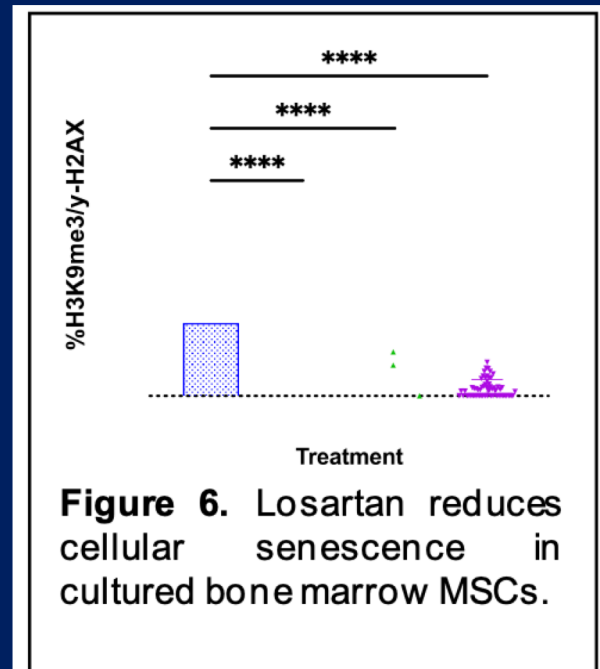
Losartan appears to decrease left ventricle fibrosis in the rat model



Losartan is also a Senolytic drug:

Losartan was as effective as the senolytic fisetin at decreasing cellular senescence as measured by quantifying senescence or immunohistochemistry to H2AX and H3K9me3 (markers of cellular senescence) (**Figure 6**).

These results suggest that **Losartan**, in addition or reducing TGF- β 1 and fibrosis, may also reduce cellular senescence and inflammation.



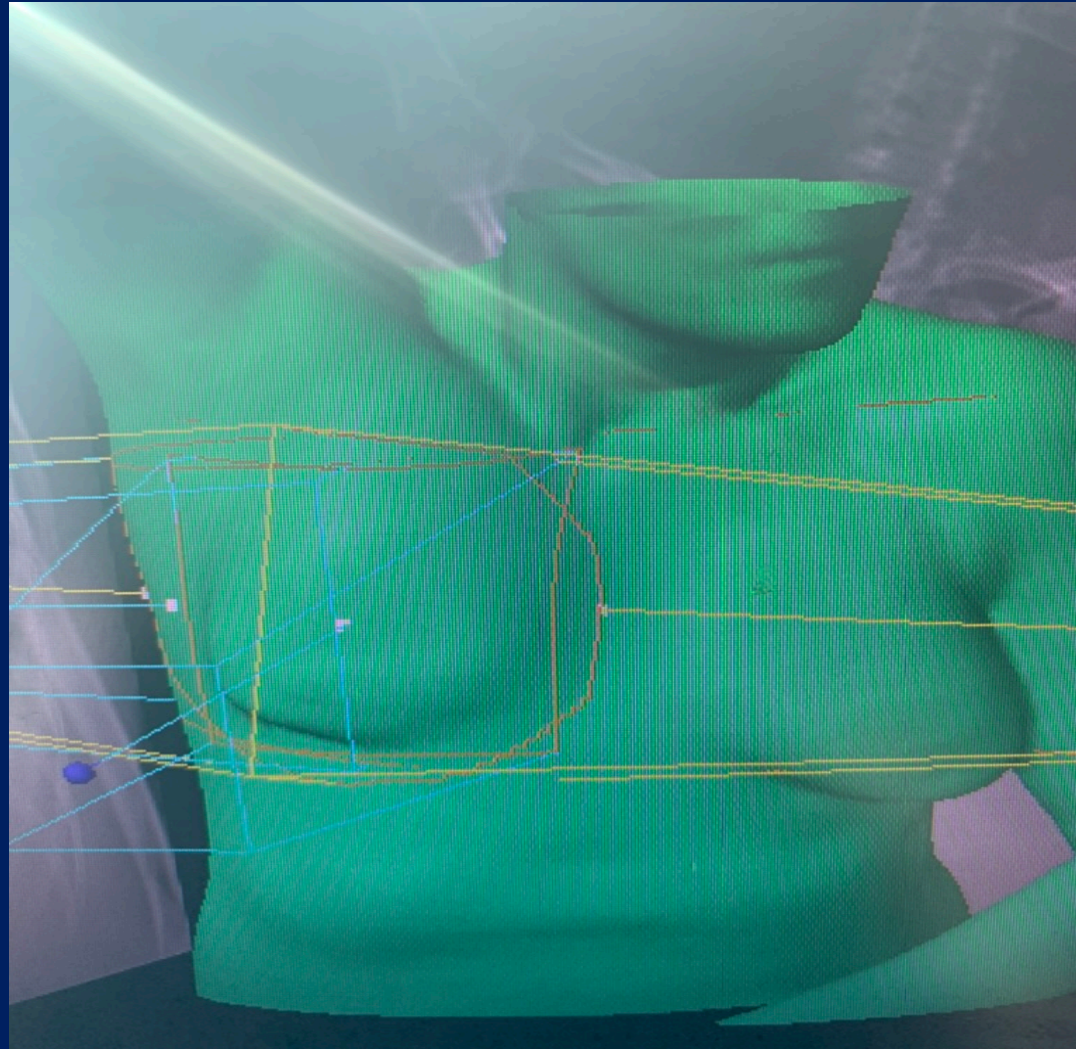
J. Huard/SPRI laboratory, 2023

Radiation-Induced Fibrosis Targeted Model

- TGF-B is a target to mitigate RIF
- Losartan is a TGF-B inhibitor
- Senescent cells and their SASP molecules lead to fibrosis
- Losartan appears to have Senolytic activity

Our Study Population:

Breast Cancer patients undergoing curative radiation therapy after surgery



Why study Losartan inhibition of Radiation Fibrosis in Breast Cancer?

- Second most common cancer in women
- Majority of breast cancer patients get Radiation
- Important QOL outcomes
- 20 years of study with validated endpoints
- Measurable
- Palpable
- Radiographically defined
 - CT scans of chest
 - Mammograms

Specific Aim: To determine in a randomized, placebo-controlled trial whether Losartan will reduce radiation-induced fibrosis in the breast and the lung and improve clinical outcomes in irradiated breast cancer patients.

Hypothesis 1: Losartan will decrease RIF in the **breast** of irradiated breast cancer patients and improve cosmetic outcomes relative to Placebo treatment.

Hypothesis 2: Losartan will decrease RIF in the **lung** of irradiated breast cancer patients *relative to* Placebo treatment.

Hypothesis 3: The development of fibrosis in the **breast and the lungs** will be associated with each other and with **increased levels of TGF- β 1, cellular senescence/inflammation**. Losartan will inhibit senescence and TGF- β 1 levels in serum providing a possible mechanistic explanation for reducing RIF (breast/lung) in breast cancer patients.

Breast Cancer Patients after surgery



Losartan

Placebo

Assessments to determine outcomes:

1. **Physical Exam** to assess breast fibrosis
2. **CT scans** of the chest to assess lung fibrosis
3. **Mammograms** to measure shrinkage
4. **Blood test** to analyze Senescence and TGF-B levels, SASP
5. **Patient Report Outcomes**

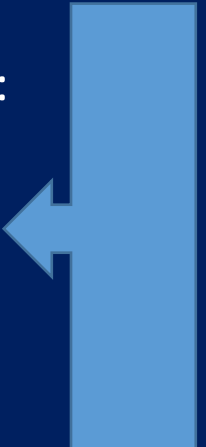
Time points:

Start RT

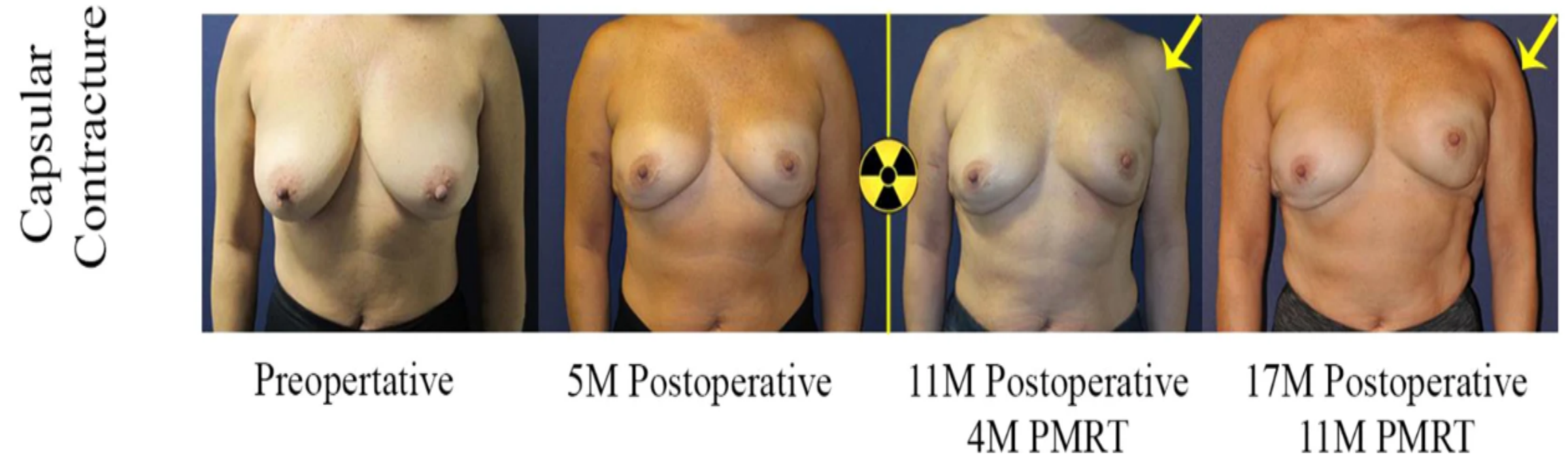
3 mos

6 mos

12 mos



Hypothesis 1: Losartan will decrease RIF in the **breast** of irradiated breast cancer patients and improve cosmetic outcomes relative to Placebo treatment.



Capsular Contracture after Mastectomy and Radiation
Presents with pain, breast firmness, distortion, and displacement

This fibrosis related complication requires surgical revision:

50-68 % of patients

Hypothesis 2: Losartan will decrease RIF in the **lung** of irradiated breast cancer patients *relative to* Placebo treatment.



Primary Reference Point		
ID	Planned Dose per Fraction [cGy]	Planned Total Dose [cGy]
L_SClav	200.0	5000.0
L_Breast	200.0	5000.0



89% incidence in radiation-induced lung fibrosis 12 months post breast radiation

Hypothesis 3: The development of fibrosis in the breast and the lungs will be associated with each other and with increased levels of TGF- β 1, cellular senescence/inflammation.

- SPRI has developed a unique method to test for senescence in human serum
- Losartan will inhibit senescence and TGF- β 1 levels in serum
- This provides mechanistic explanation for the development of post radiation inflammation and fibrosis

The Innovative Complementary Team

SPRI

Dr. Johnny Huard Lead Scientist, career in anti-fibrotics

Dr. Marc Philippon, Pioneer using Losartan in Ortho

Dr. Scott Tasman, Clinical Trial Expertise in Imaging

Dr. Chelsea Bahney, Program Director for Regenerative Therapeutics

Grant Doman, Biostatistical research expertise

Shaw Cancer Center

Dr. Julie Barone Breast surgery

Dr. Jinnah Phillips Breast Imaging

Dr. Alec Urquhart Medical Oncology

Dr. Jason Martin Plastic Surgery

Dr. Patricia Hardenbergh Radiation Oncology

Flipping the Model of Cancer Research

- 85% of cancer patients are treated in a community cancer center.
- Community cancer centers are an underrepresented population in clinical research.
- 34% of patients at Vail Health Shaw Cancer Center were enrolled on a clinical trial last year.
- Culture of improving cancer care at Vail Health Shaw Cancer Center

INNOVATION:

- **The problem we will solve:** is that breast cancer patients' breasts can become cosmetically unacceptable after radiation and that there is almost universal scarring in their lungs.
- We are testing an old drug (losartan) with novel applications.
- We are building on the experience and laboratory expertise and clinical trials using Losartan with our **SPRI colleagues** to **apply Sports Medicine to Oncology**

The Real INNOVATION:

- RIF occurs in virtually every site which undergoes radiation for the treatment of cancer
- If successful, the results in this study population of breast cancer patients will be tested in other patient populations, in other irradiated disease sites and it **will improve lives and save lives and change the future of radiation oncology**

Many Clinical Examples of Radiation-Induced Fibrosis

because it effects every site we treat:

- Lung cancer.....difficulty breathing
- Breast Cancer.....breast shrinkage, lung scarring
- Prostate Cancer.....loss of sexual functioning, incontinence
- Head and Neck Cancer.....difficulty swallowing, neck muscle stiffening
- Brain Tumors.....loss of intellect and memory
- GYN Cancer.....vaginal stenosis, urinary leaking
- Sarcomas.....muscle stiffening, lymphedema
- Esophageal Cancer.....strictures, difficulty swallowing
- Anal Cancer.....Pain with bowel movements

And then Radiation Therapy will Save Lives Without Changing Lives



Saves limbs
Alternative to Surgery
Saves Lives

Saves breasts
Saves voices
Kills Cancer