Advances in Lymphatic Imaging and Lymphedema Treatment

10/12/22

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Body MR Fellow

Stanford MEDICINE Radiology

STANFORD BYERS CENTER FOR BIODESIGN CELEBRATING 20 YEARS

Lymphatic Education & Research Network Centers of Excellence

LD Comprehensive Center of Excellence

Disclosures

- Off label – this presentation will discuss off label use of:
  - Gadolinium contrast agents
  - Ferumoxytol

Overview

- Background on Lymphatic Disease and Lymphatic Imaging
- Drug Trial
- MR Lymphangiography
  - DARC-MRL
    - Technique
    - Staging
  - Subcutaneous Thickness Fraction
  - ION-MRL
- Teaser: Novel Treatment for Lymphedema

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- “It is simple. Any doctor could have done it . . . You cannot help that which you have not sought to understand.”

  - The Healer

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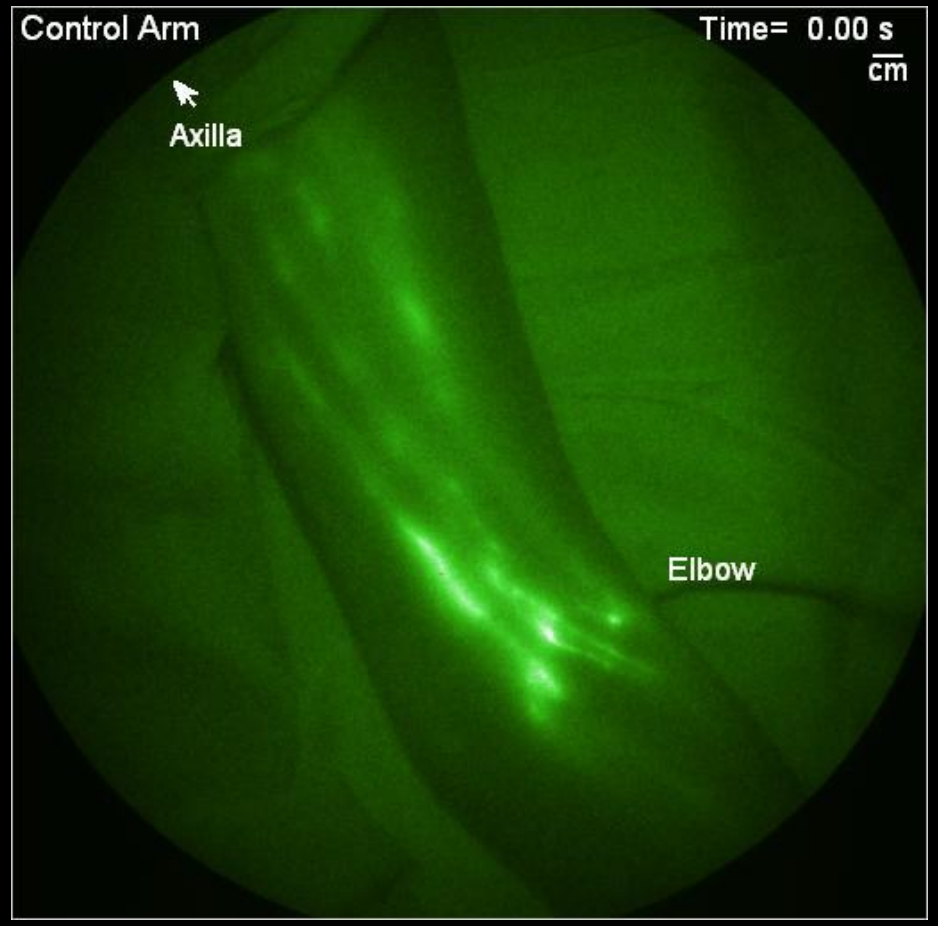
The Lymphatic System

- The Lymphatic Continuum:
  - Lymphedema
  - Chylothorax
  - Chylous ascites
  - Cancer metastasis
  - Dementia
  - Autoimmune Disease
  - Lymphatic Vascular Malformations
  - Obesity Metabolic Syndrome
  - Lipidema
  - Generalized Lymphatic Anomalies
  - Organ Transplantation
  - CAD & CHF
  - . . .



Rockson SG. Comorbidity and Lymphatic Disease: The Lymphatic Continuum Re-Examined. Lymphatic Research and Biology. 2021.

A supplemental video from the 2012 review by E.M. Sevick-Muraca, "Translation of Near-Infrared Fluorescence Imaging Technologies: Emerging Clinical Applications," from the Annual Review of Medicine: annualreviews.org/doi/abs/10.1146/annurev-med-070910-083323

Lymphedema

"It's a very rare disease—it doesn't have a cure. It doesn't even have a spokesperson."

L

t have a cure.
person."

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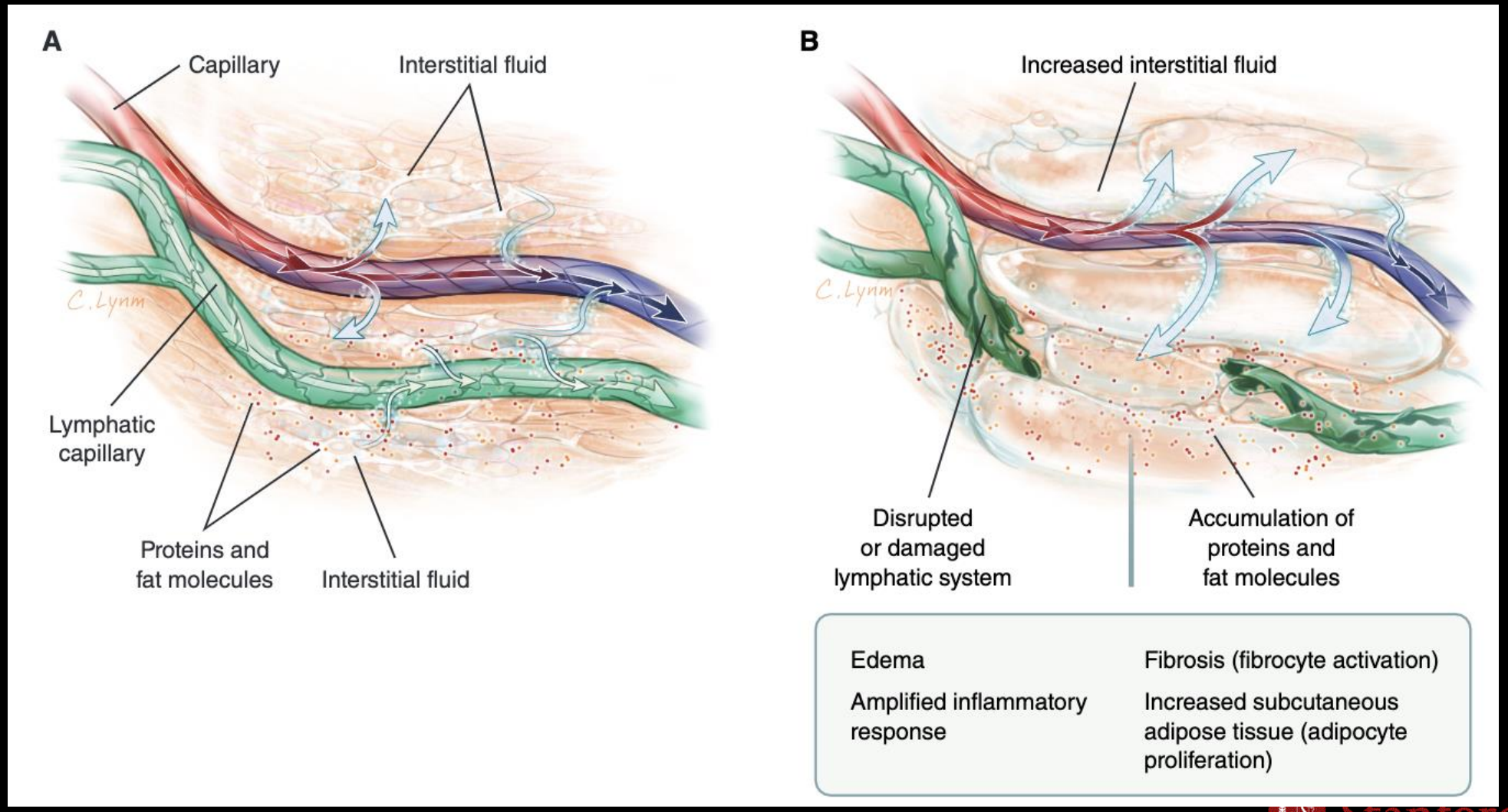
Success!

- 

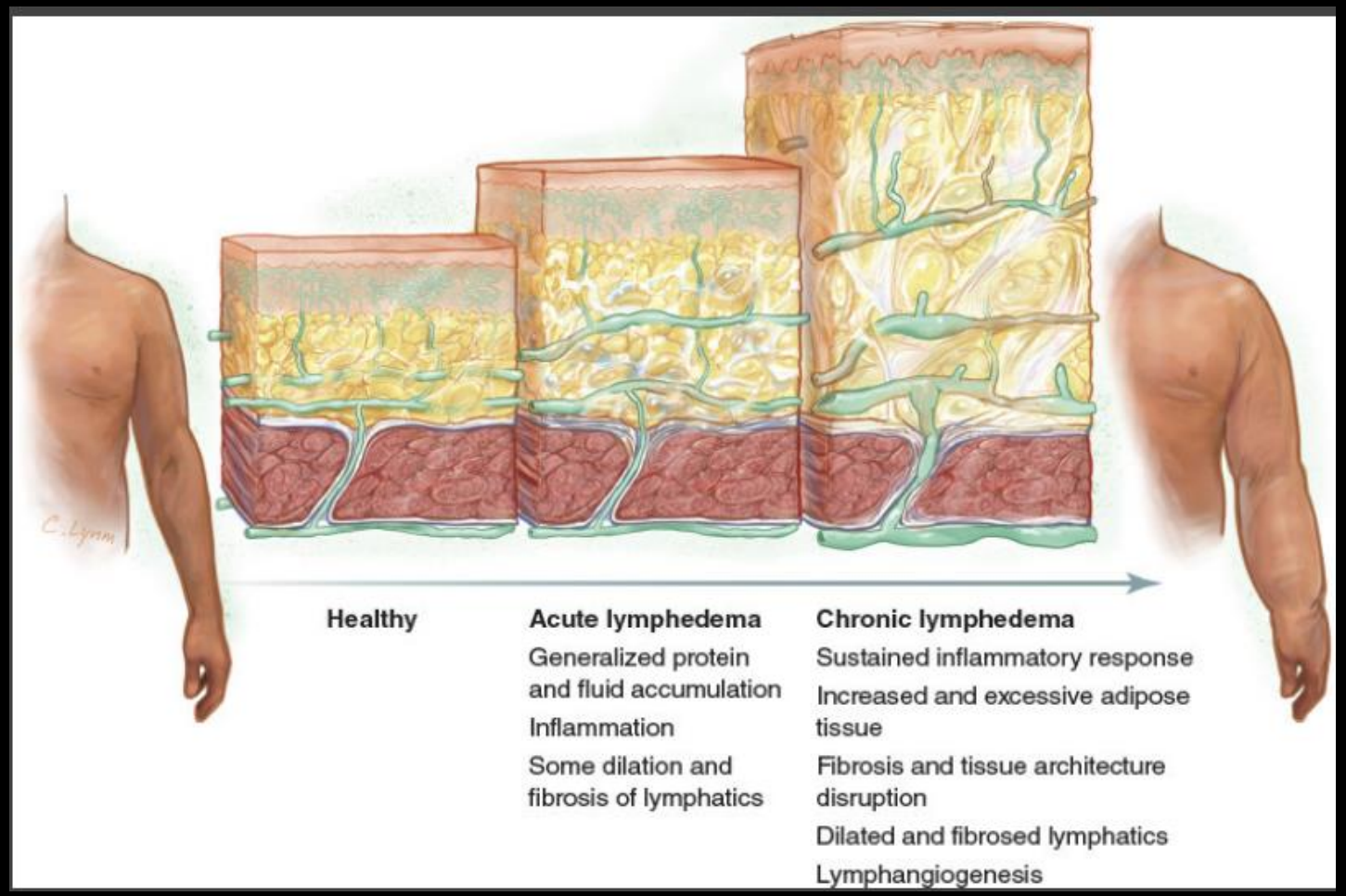
- Lymphatic diseases and lymphedema added as eligible categories for research under the Department of Defense's Peer-Reviewed Medical Research Program ($400 million-dollar annual budget)

Lymphedema



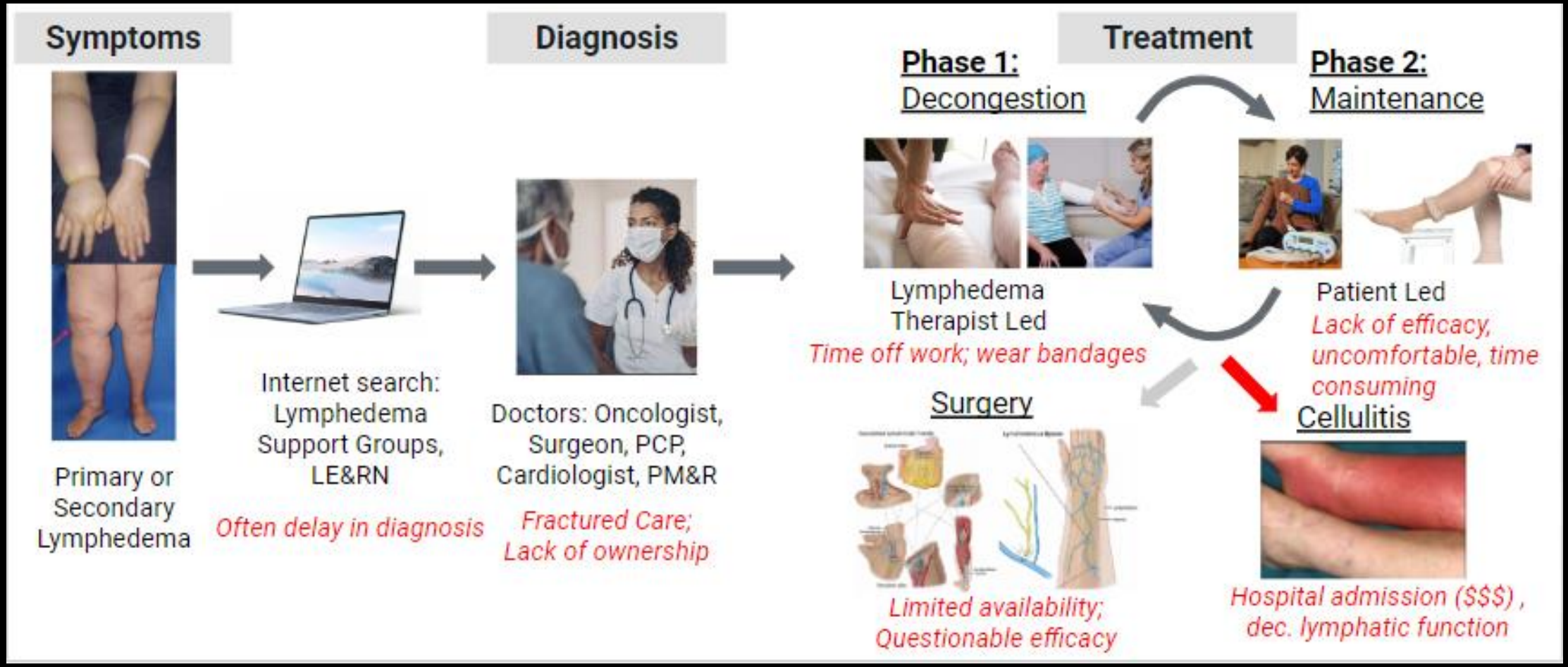
Neligan PC, Masia J, Piller NB. *Lymphedema : Complete Medical and Surgical Management*. NEW YORK: Thieme; 2015. http://search.ebscohost.com.foyer.swmed.edu/login.aspx?direct=true&db=nlebk&AN=1696430&site=eds-live&scope=site. Accessed May 29, 2020.

Lymphedema



Overview of the Lymphatic System. In: Neligan P, Masia J, Piller N, ed. Lymphedema: Complete Medical and Surgical Management. 1st Edition. Thieme; 2015. doi:10.1055/b-004-140253

Lymphedema Cycle of Care



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Lymphedema Staging

TABLE 1-1 International Society of Lymphology Lymphedema Staging

Stage*	Clinical Description
0	Latent or subclinical condition in which swelling is not yet evident despite impaired lymph transport with subtle changes in tissue fluid or changes in subjective symptoms. It may exist months or years before overt edema occurs.
I	Early accumulation of fluid relatively high in protein content, which subsides with limb elevation. Pitting may occur.
II	Limb elevation alone rarely reduces tissue swelling, and pitting is common.
III	Lymphostatic elephantiasis in which pitting can be absent and trophic skin changes, such as acanthosis, fat deposits, and warty overgrowths, develop.

*Other classifications/authors use arabic numerals for these stages: 0, 1, 2, 3.

Neligan PC, Masia J, Piller NB. *Lymphedema : Complete Medical and Surgical Management*. NEW YORK: Thieme; 2015. http://search.ebscohost.com.foyer.swmed.edu/login.aspx?direct=true&db=nlebk&AN=1696430&site=eds-live&scope=site. Accessed May 29, 2020.

Clinical Need: Better quantification of lymphatic function

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JCI insight

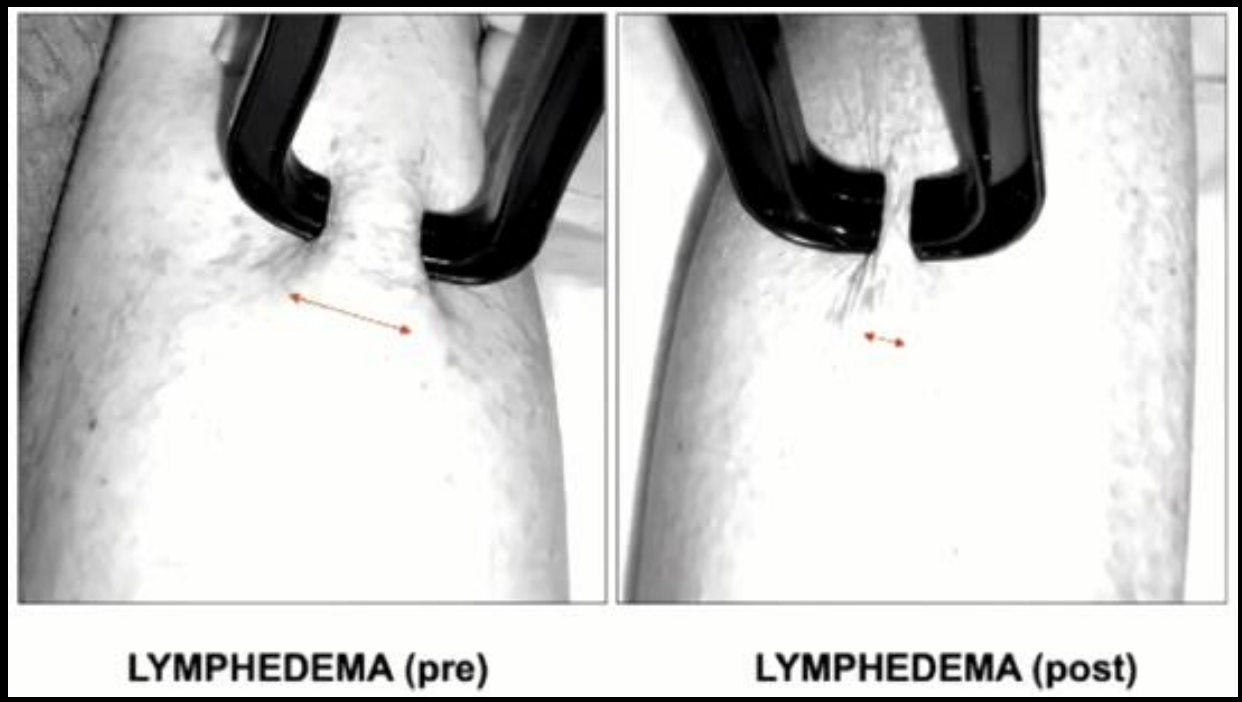
CLINICAL MEDICINE

Pilot studies demonstrate the potential benefits of antiinflammatory therapy in human lymphedema

Stanley G. Rockson,[1] Wen Tian,[2] Xinguo Jiang,[2] Tatiana Kuznetsova,[3] Francois Haddad,[1] Jamie Zampell,[4] Babak Mehrara,[4] Joshua P. Sampson,[1] Leslie Roche,[1] Jinah Kim,[5] and Mark R. Nicolls[2]

[1]Department of Medicine, Stanford University School of Medicine, Stanford, California, USA. [2]Department of Medicine, VA Palo Alto Health Care System/Stanford University, Palo Alto, California, USA. [3]Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Belgium. [4]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York City, New York, USA. [5]Department of Pathology, Stanford University School of Medicine, Stanford, California, USA.

*Ketoprofen issued BLACK BOX WARNING for increased risk of heart attack and stroke



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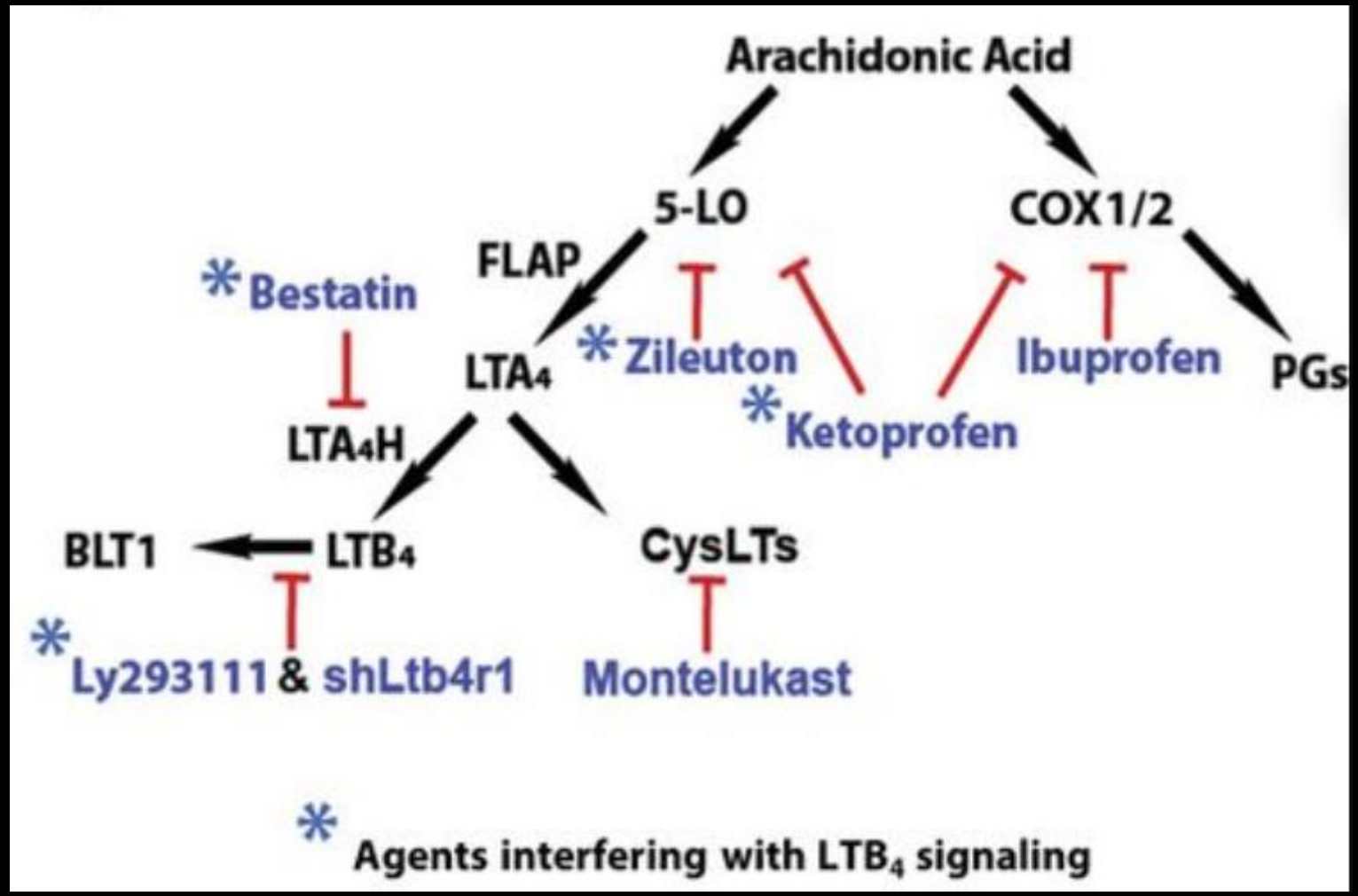
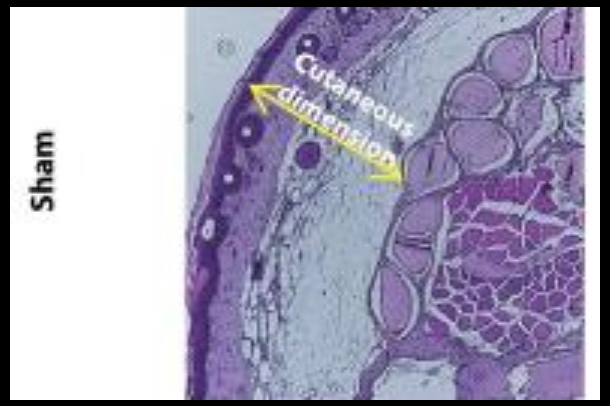
Eicosanoid Inflammatory Pathway

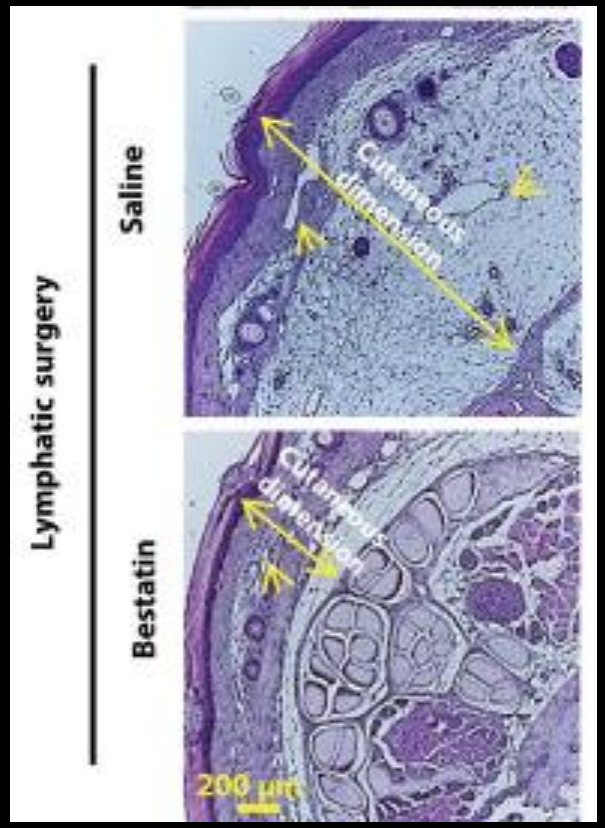


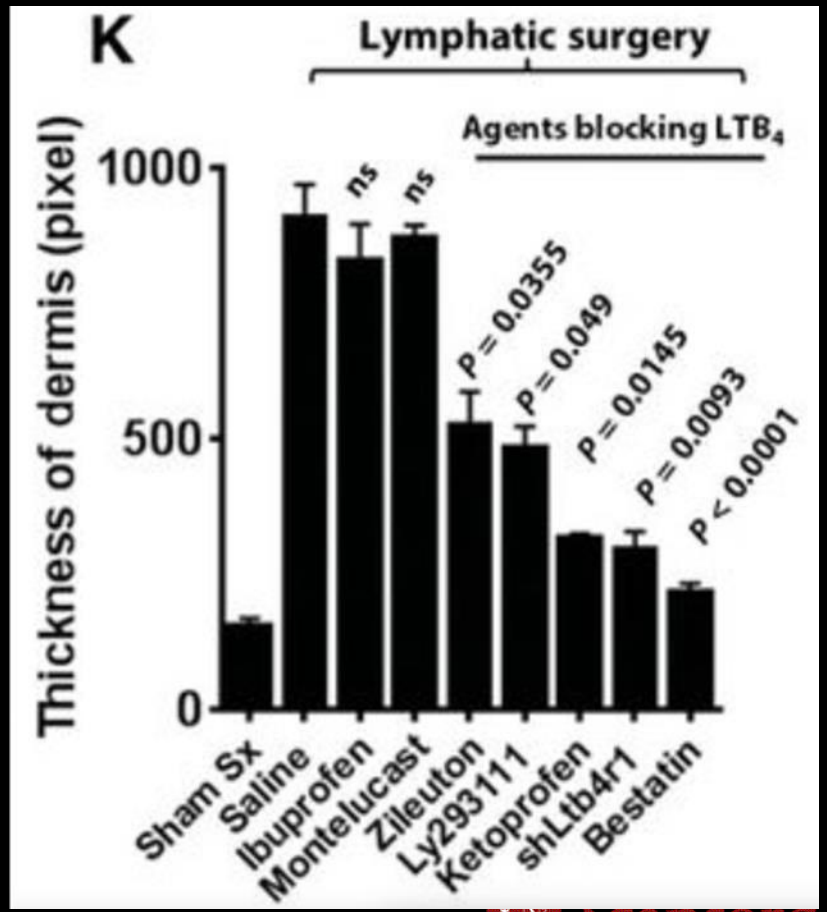
Leukotriene B_4 antagonism ameliorates experimental lymphedema

WEN TIAN, STANLEY G. ROCKSON, XINGUO JIANG, JEANNA KIM, ADRIAN BEGAYE, ERIC M. SHUFFLE, ALLEN B. TU, MATTHEW CRIBB, ZHANNA NEPIYUSHCHIKH, [...] MARK R. NICOLLS +8 authors Authors Info & Affiliations

SCIENCE TRANSLATIONAL MEDICINE • 10 May 2017 • Vol 9, Issue 389 • DOI: 10.1126/scitranslmed.aal3920







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Human Lymphedema Acebilustat Trial (HEAL) (NCT05203835)

- Acebilustat is an orally bioavailable, small molecule inhibitor of the enzyme leukotriene A4 hydrolase (LTA4H)

Celltaxis LLC

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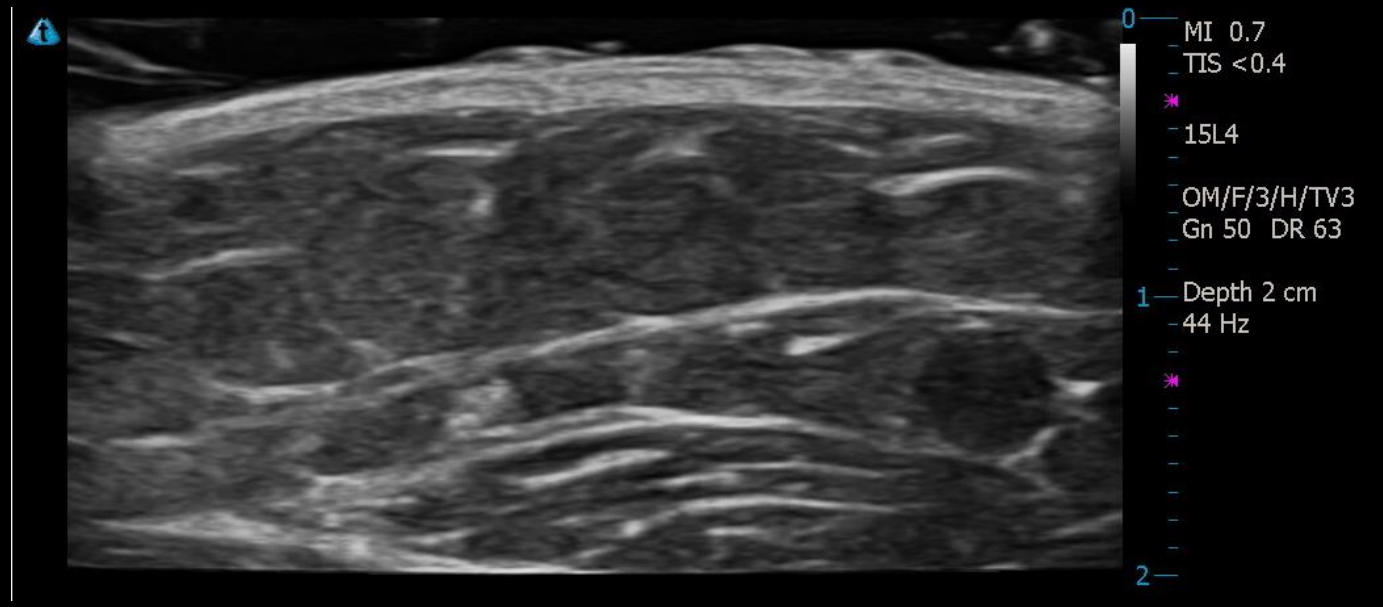
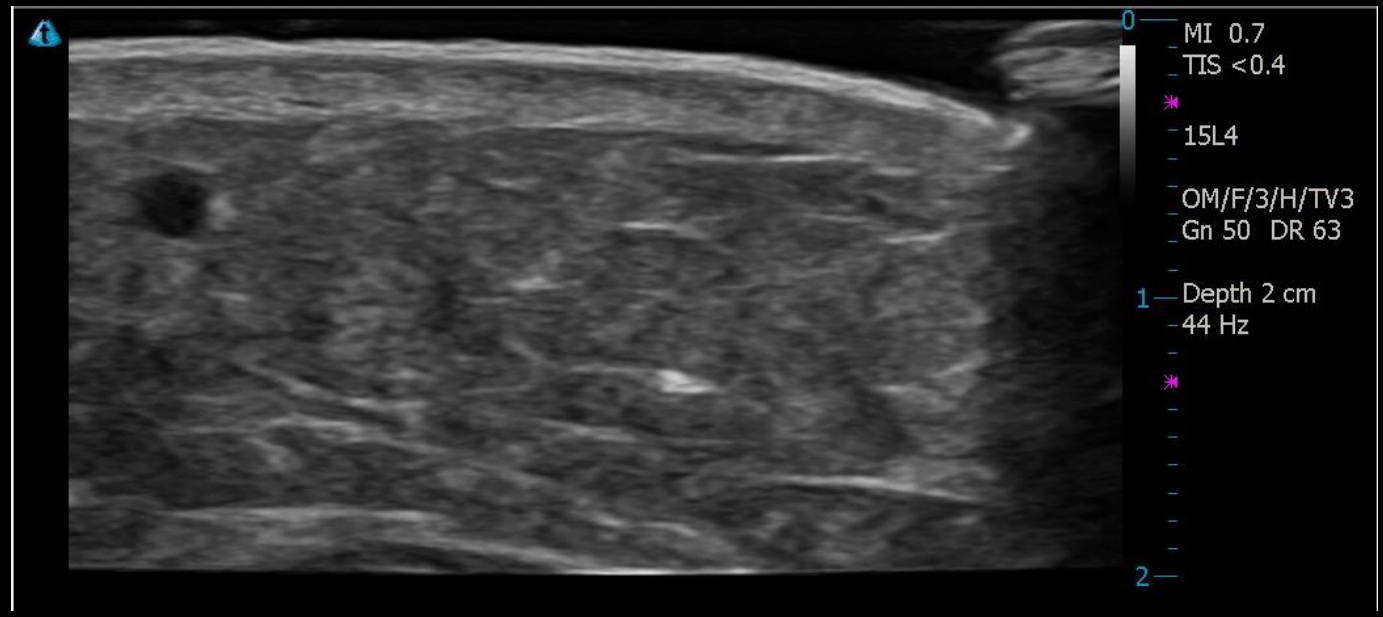
Dermal Thickness

Normal



Lymphedema



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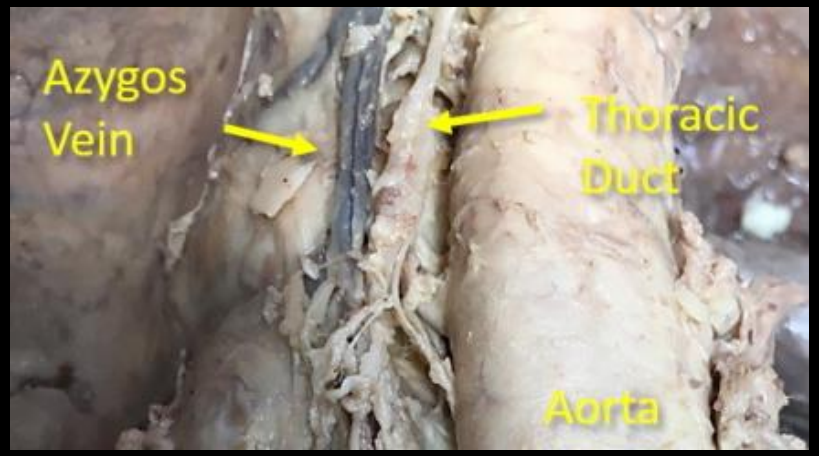
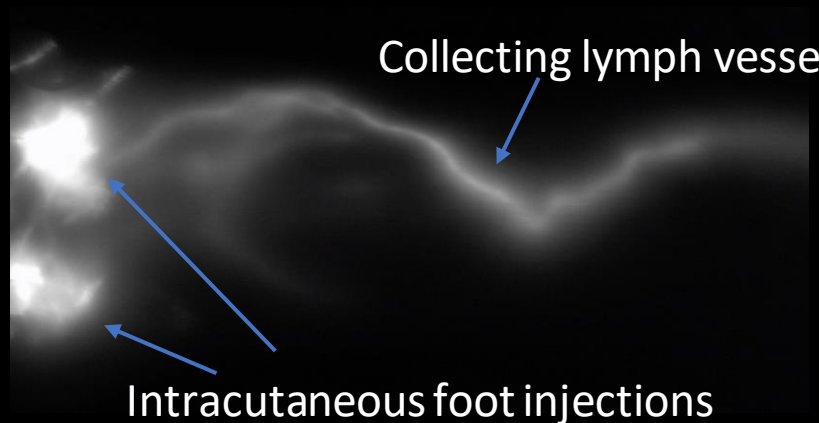
Challenges to Imaging the Lymphatic system

- Size of lymphatics:
  - Thoracic duct 2-5 mm in diameter[1]
  - Often need contrast agent
- Unidirectional System:
  - Must get contrast "upstream" of the lymphatics to be visualized
- Specific Contrast requirements:
  - 10-50 nm (Bergqvist 1987)
  - Gad ~1nm leaks out of lymphatics





[1]RC Sibley et. al. Interventional Radiology in the management of thoracic duct injuries: anatomy, techniques and results. Clinical Imaging. Mar 2017.183-192.

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MR Lymphangiography (MRL) Techniques

- Non-contrast MRL
- Intranodal MRL
  - Pediatric Central Lymphatics
  - Typically, with General Anesthesia
- Contrast Enhanced Peripheral MRL:
  - Gad-MRL
    - Venous contamination
  - DARC MRL (Maki et. Al. 2016)
    - IV Ferumoxytol suppresses venous signal

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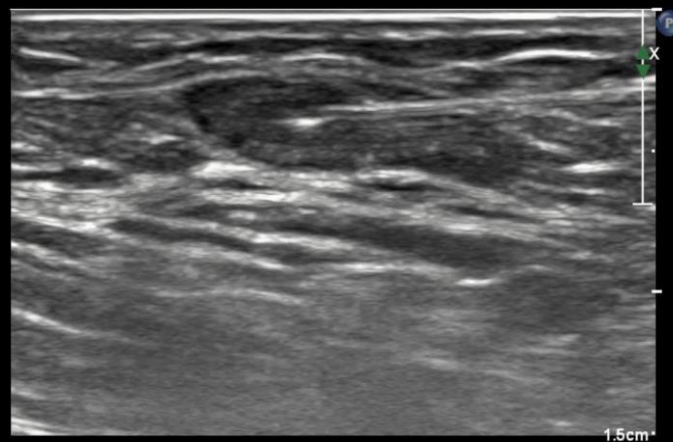
Intranodal MRL

- 4 yo M with Single ventricle physiology status post fontan complicated by protein losing interopathy



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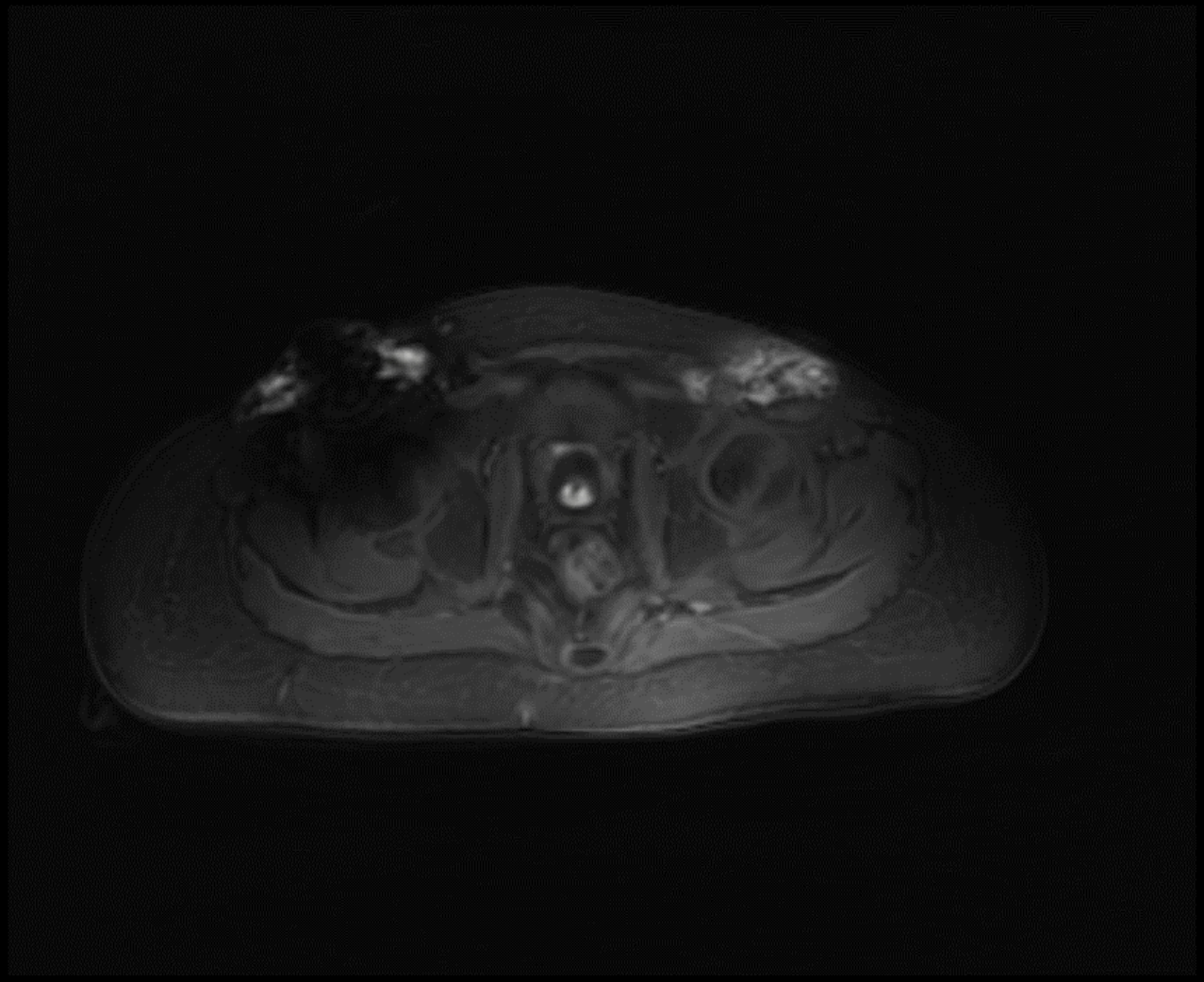
Intranodal MRL



Ax T1 UTE

IR Lymphangiogram with Lipiodol

- In remission with stable albumin levels and symptoms
- Can consider glue embolization if effect diminishes.

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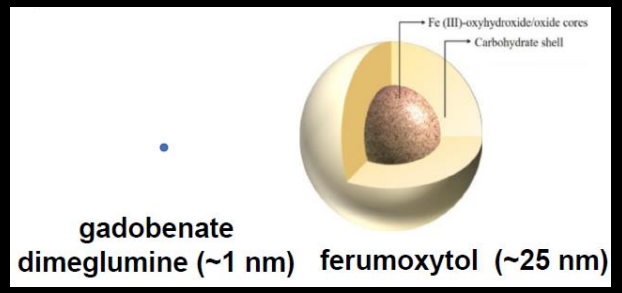
IV Ferumoxytol

+

GAD-MRL

=

DARC-MRL



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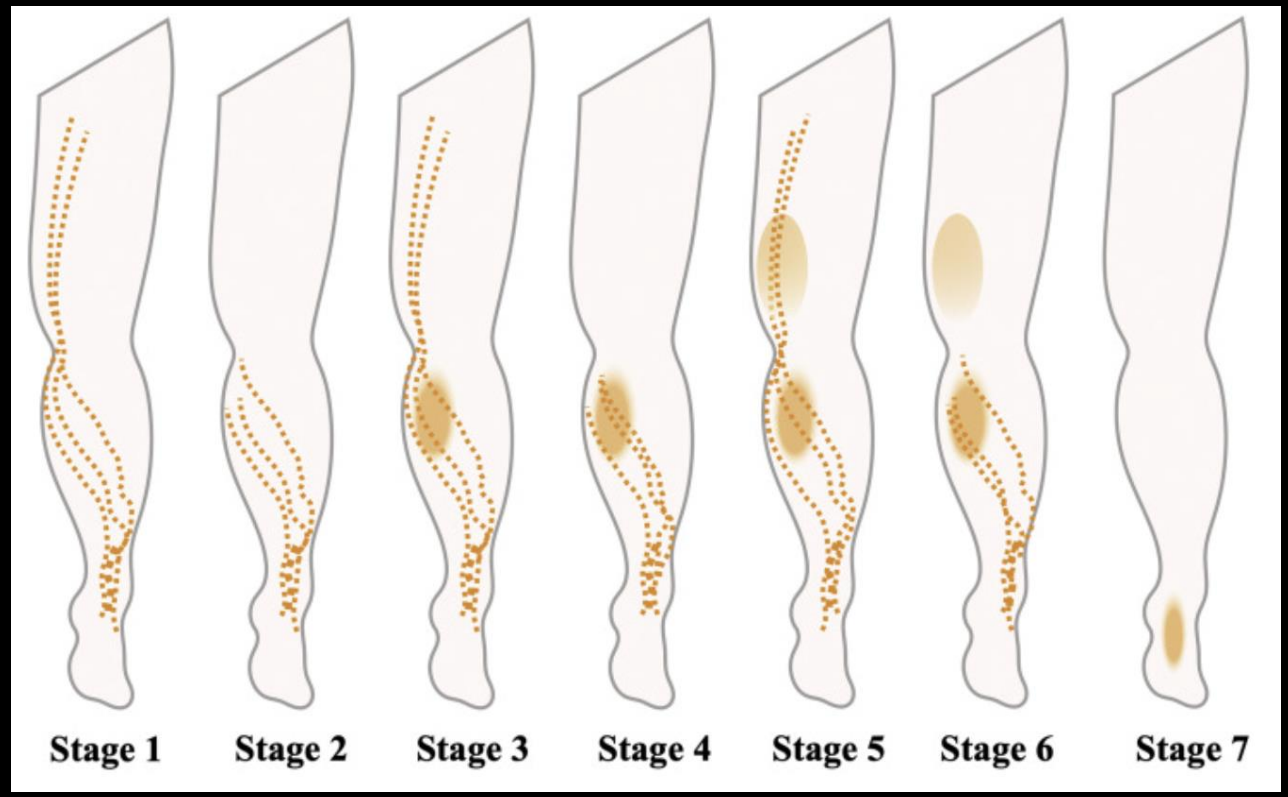
Suspected Upper extremity lymphedema	Non-contrast T2w FSE	Dermal Rim Sign • honeycombing • hyperintense signal of overlying thickened skin • fluid signal within the subcutaneous tissue	ISL Stage Dermal Backflow on Lymphoscintigraphy L-Dex	64
Lower Extremity lymphedema	Post-contrast T1w 3D SPGR	Inguinal node contrast ratio (SI post-contrast/SI pre-contrast) at 5 min	ISL Stage	121
Lower Extremity lymphedema	T1 GRE	Fluid accumulation grade 0 = no fluid 1 = honeycombing/reticular pattern of fluid within the subcutaneous fat 2 = continuous visible stripe of fluid between the fat and investing muscle fascia. Fat Accumulation Grade 0 = no excess fat 1 = fat accumulation less than twice the width of the widest fat stripe on the unaffected side 2 = fat accumulation greater than twice the width of the widest fat stripe on the unaffected side	ISL Stage	66
Lower Extremity lymphedema	Post-contrast 3D Dixon	MRL Stage 1: no DBF, and lymph vessels are visible above the knee joint. Normal, nondilated lymphatic vessels can be seen above the knee joint and are slightly visible in the groin. 2: no DBF, and lymph vessels above the knee joint are not visible. Normal, nondilated lymphatic vessels can be seen below the knee joint. 3: DBF appears below the knee joint, and lymph vessels are seen above the knee joint. 4: both DBF and lymph vessels are seen below the knee joint. 5: DBF and lymph vessels are seen above the knee joint. 6: DBF is seen above the knee joint, lymph vessels are observed below the knee joint. 7: DBF appears only in the foot, and lymph vessels are not visualized proximal to the foot.	ISL Stage	113

Staging Lymphedema with DARC-MRL: Methods

- IRB approved retrospective study involving 20 patients with clinically diagnosed lymphedema
- ISL Clinical Stage: chart review
- Image Analysis:
  - Each lower limb divided into 6 regions: foot, lower leg, upper leg, lower thigh, upper thigh, and groin
  - Calculated for each limb:
    - Dermal Backflow Score: Sum of regions with dermal backflow
    - Edema Score: Sum of regions with edema
    - MRL Stage: Identical to *Soga 2021*



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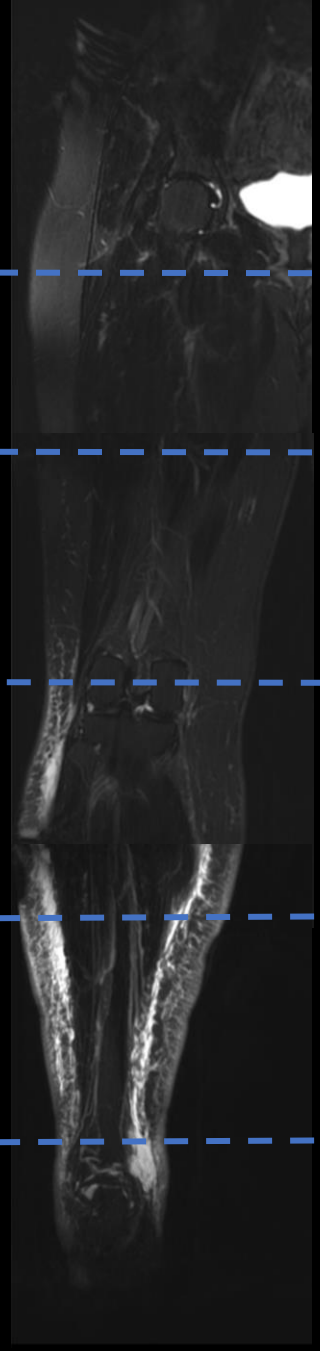
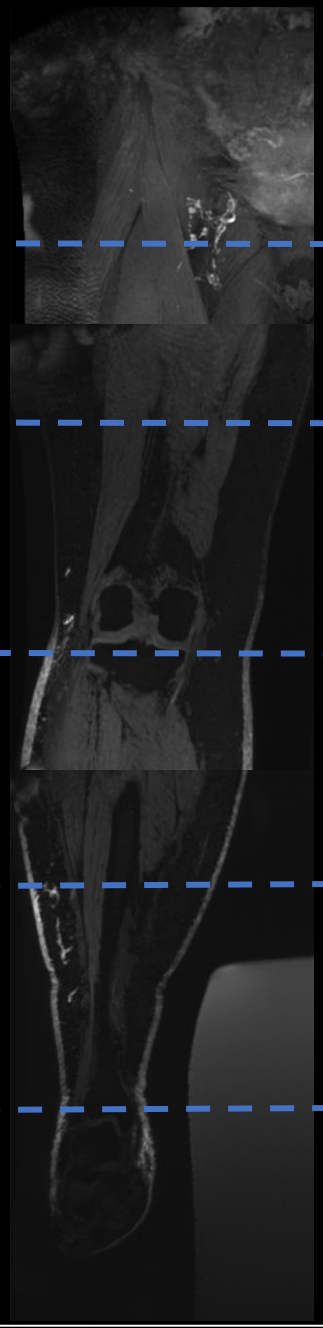
DARC-MRL Staging Example

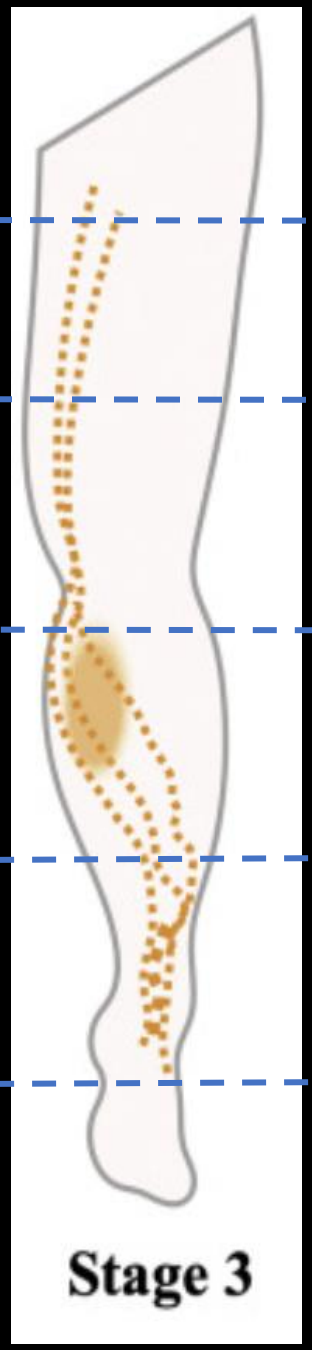
Edema	DBF
0	0
0	0
0	0
1	1
1	1
1	1



Cor T2w FS



Cor T1w FS postcon



- ISL stage 3 lymphedema
- Edema Score: 3
- DBF Score: 3
- MRL Stage: 3

*Characterizing the foot can be problematic because of injection and coil coverage

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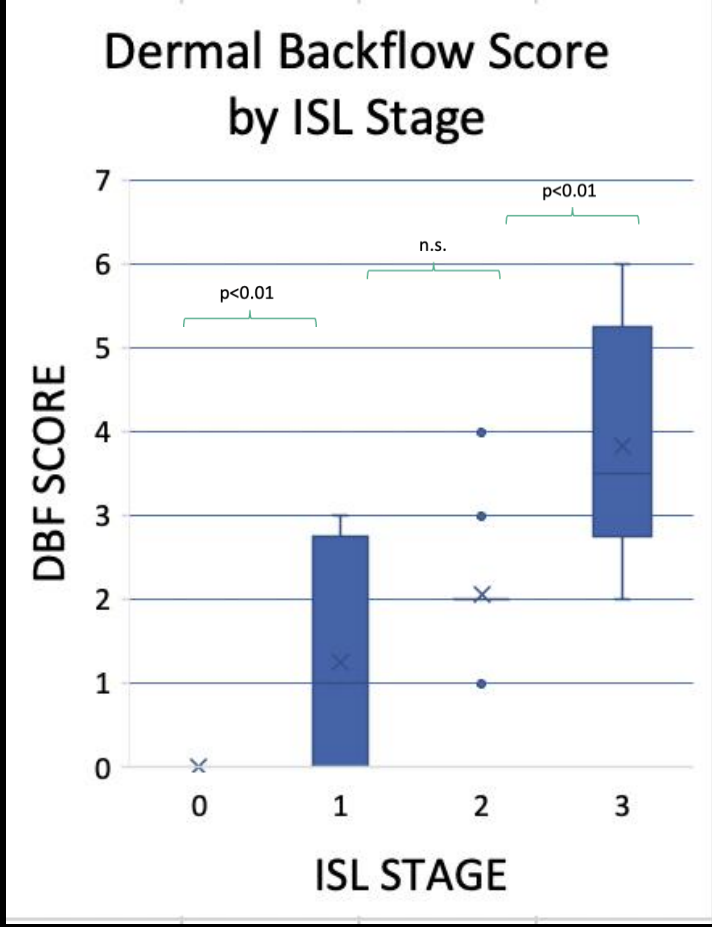
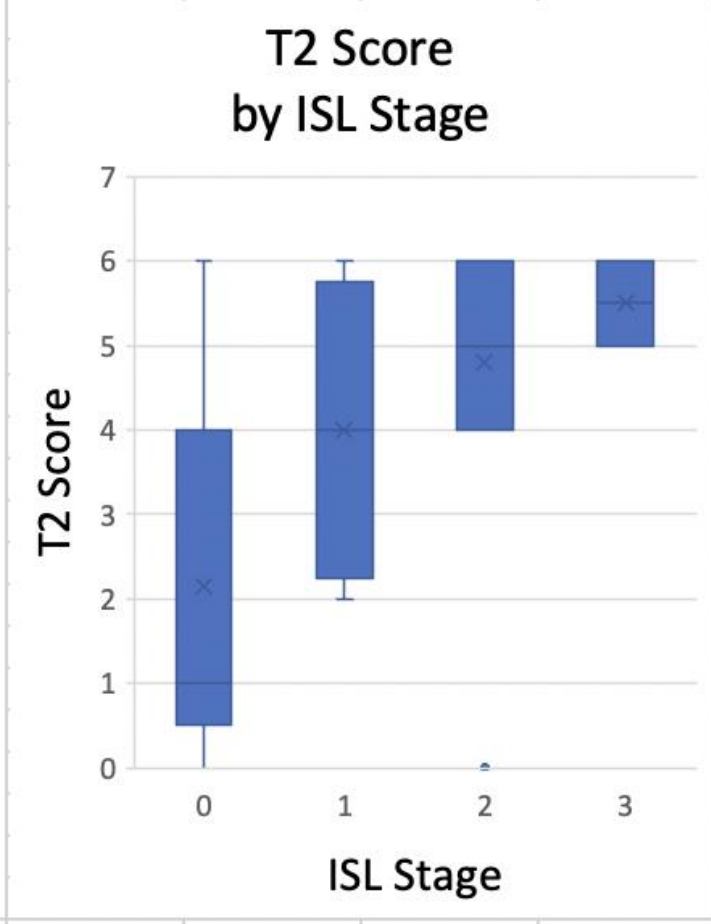
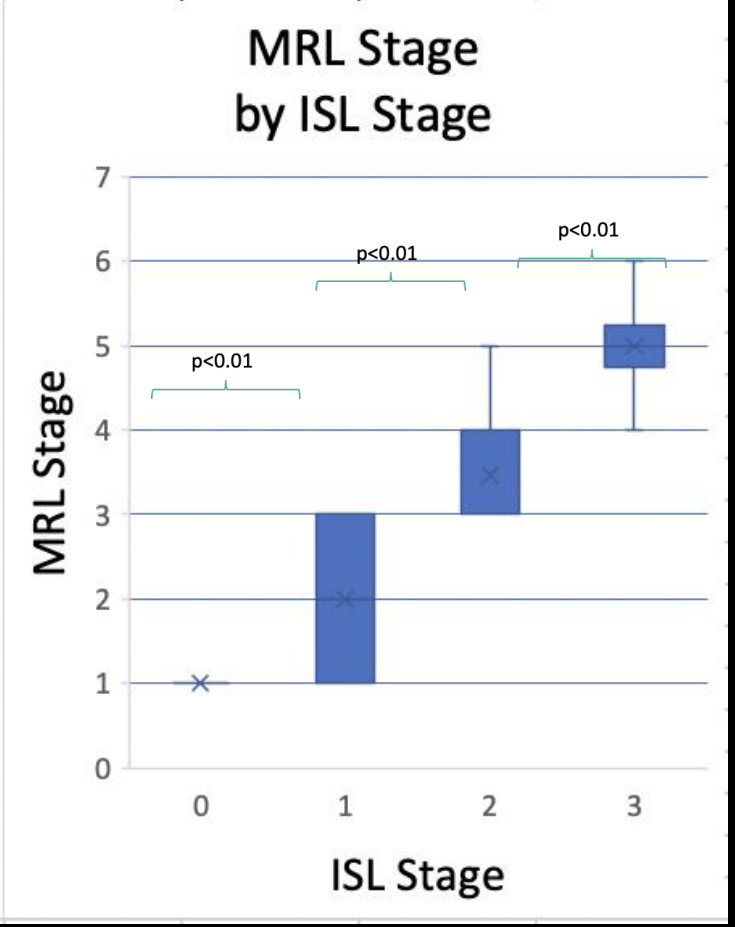


Pearson's rho of 0.85 (p<0.01)



Pearson's rho of 0.62 (p<0.01)



Pearson's rho of 0.95 (p<0.01)

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MRL Staging Conclusion

- The MRL stage, Dermal Backflow Score, and Edema Score statistically correlate with clinical lymphedema stage
- Interesting Observations:
  - Every patient with an MRL stage > 3 had an ISL Stage > 1
  - Every patient with an ISL stage of 3 had a T2 score > 4
- Next Steps: Work towards MRL interpretation algorithm and quantitative analysis

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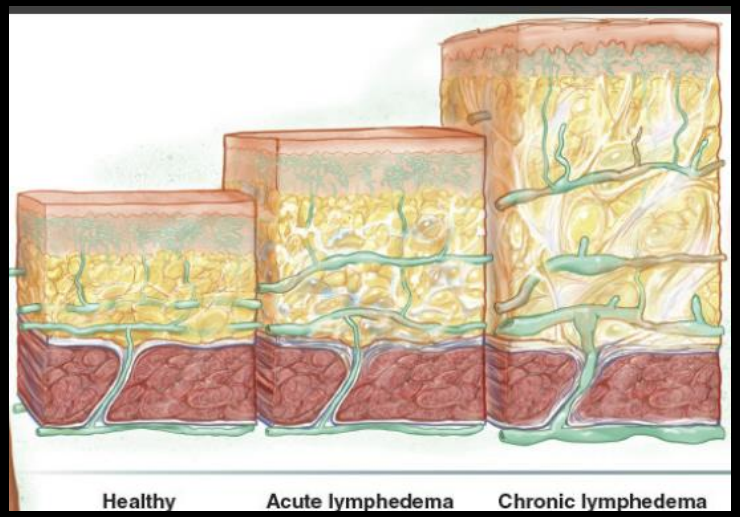

The Subcutaneous Thickness Fraction: Methods

- Retrospective analysis of 20 patients (15 male, 5 female)
- Clinically diagnosed with lymphedema (14 unilateral, 6 bilateral)
  - In patients with unilateral lymphedema, the contralateral leg was given an ISL stage 0
- Underwent Clinical MR Lymphangiography

Sequence	Parameters	Acquisition Time
T1-weighted 3D SPGR	DIXON fat separation, TE 1.1/2.2 ms, TR 5-15, Flip Angle 15°, matrix 320 x 320, slice thickness 1.6 mm, FOV 40-42 cm acquired on a 3T magnet, GE Signa Architect	~5 min

- International Society of Lymphology Clinical Stage was obtained from the clinical record

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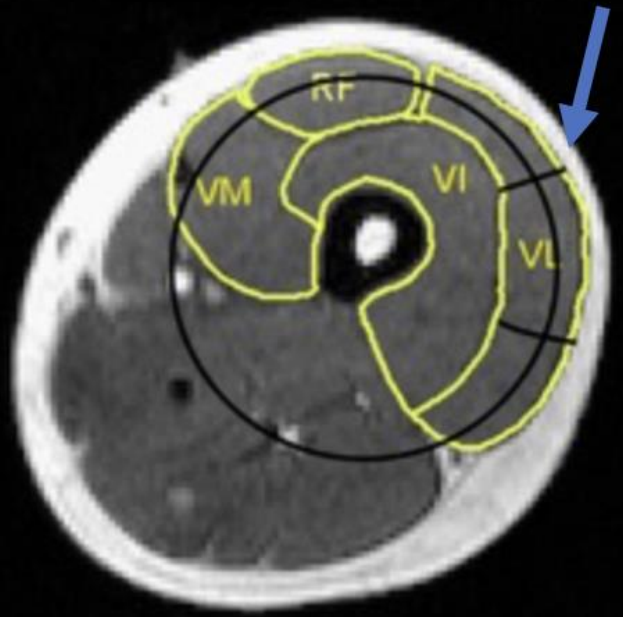
Mid-Thigh Measurements

- Thigh subcutaneous thickness fraction = subcutaneous thickness/(subcutaneous + muscle thickness)
- Measured at the distal aspect of the adductor longus; anterior 1/3 line of vastus lateralis



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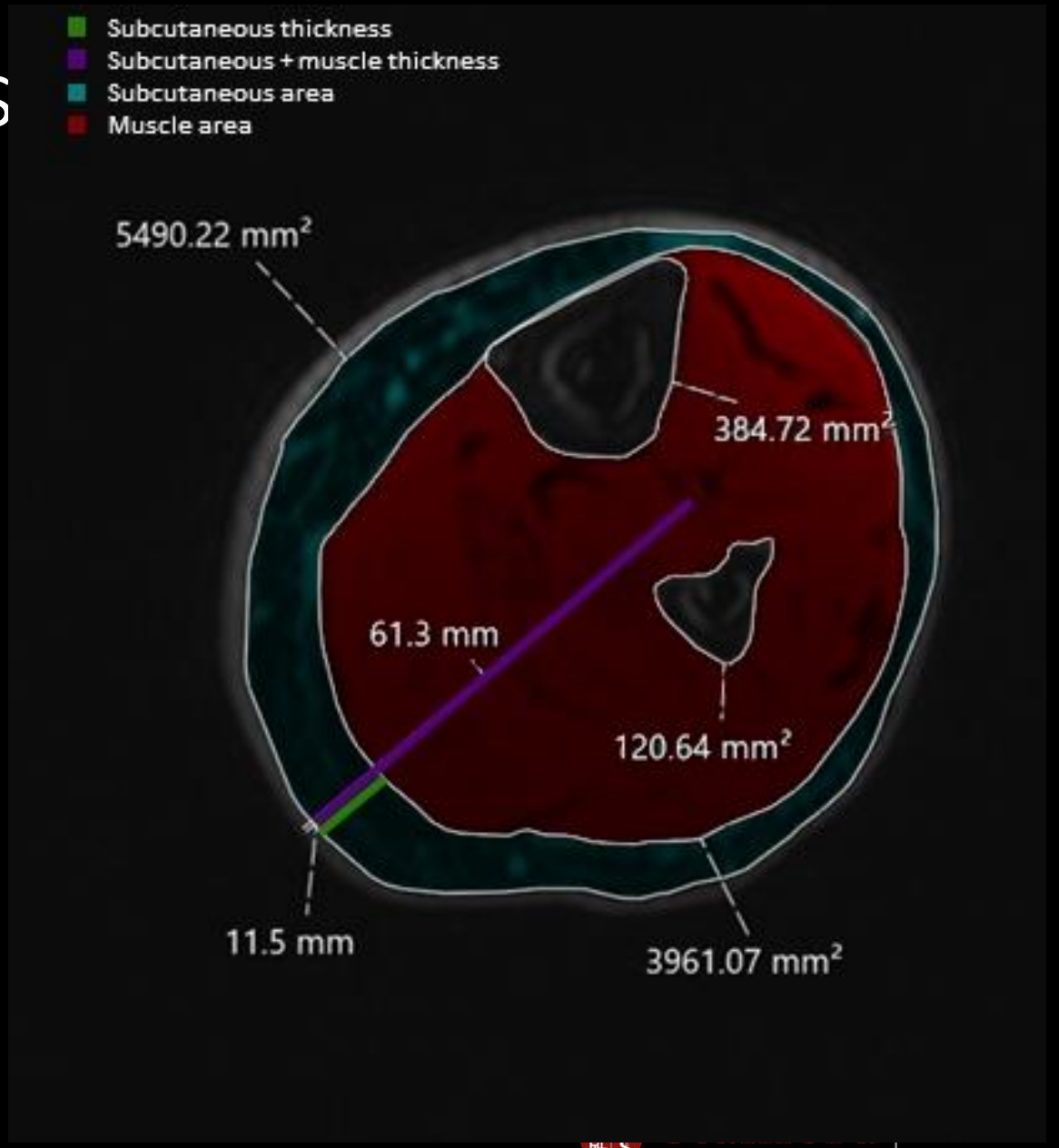
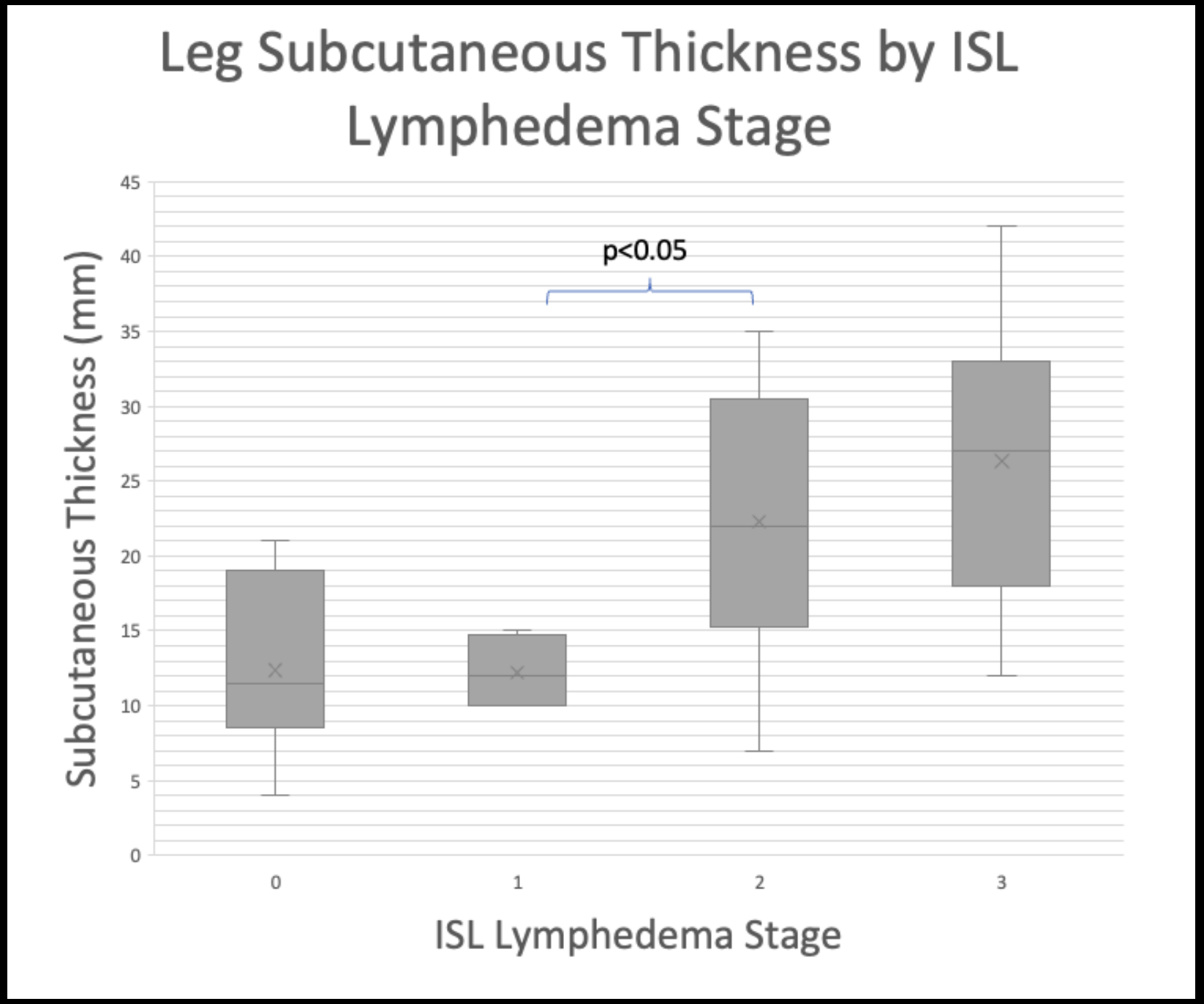
Mid-Calf Measurements

- Calf subcutaneous thickness fraction = subcutaneous thickness/(subcutaneous + muscle thickness)
- Measured at the distal margin of the gastrocnemius muscle belly along the line perpendicular and posterior to the interosseous septum.





- Strong positive correlation with a Pearson's rho of 0.59
- A statistically significant difference was observed between ISL lymphedema stage 1 and stage 2

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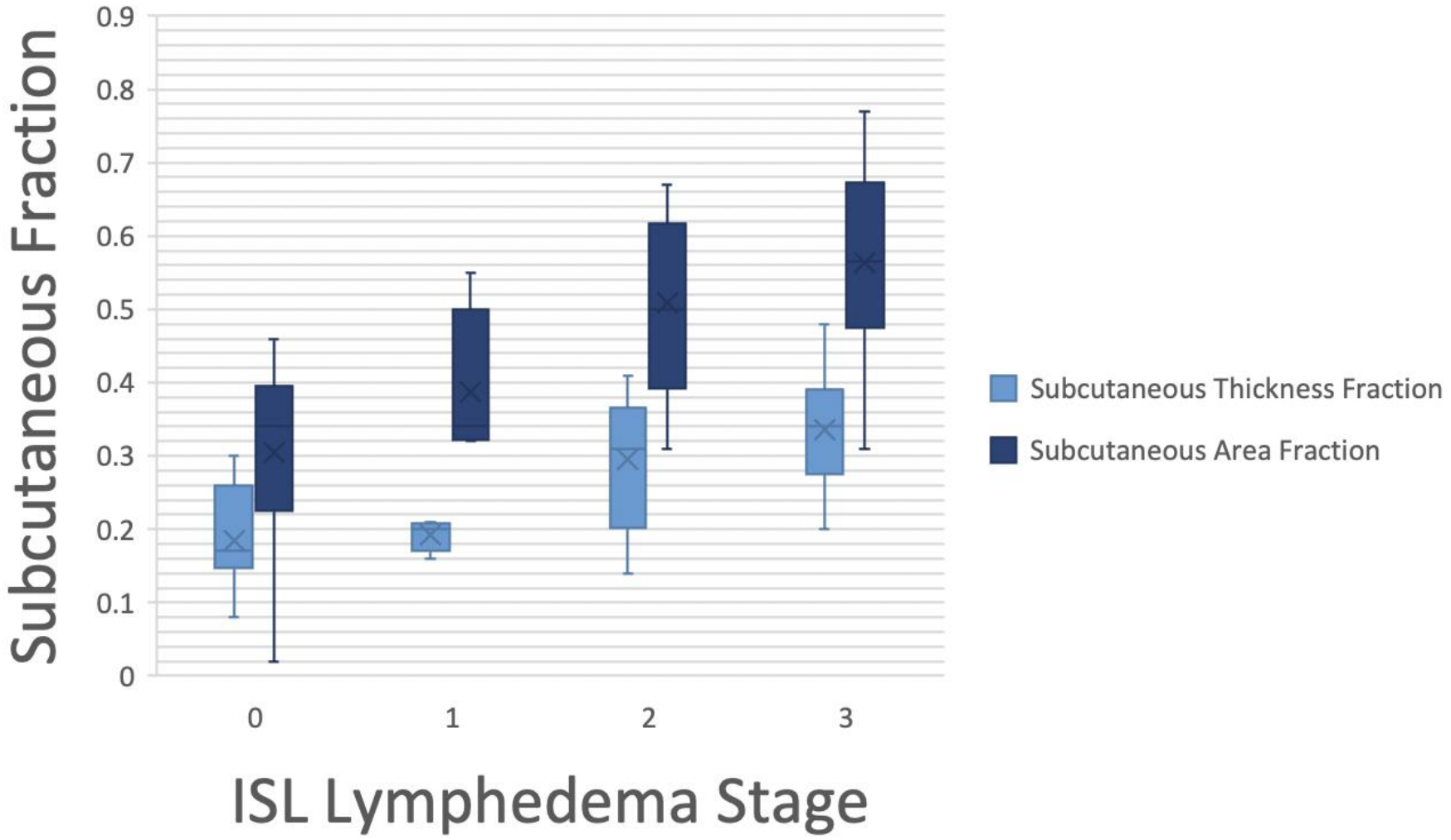
Leg Subcutaneous Thickness and Area Fractions by ISL Lymphedema Stage



- A strong positive correlation was observed for both measures with a Pearson's rho of 0.60 for thickness fraction and Pearson's rho of 0.60 for the area fraction
- For the thickness fraction a statistically significant difference was observed between ISL stage 1 and 2.

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Assessed Parameters and Clinical Stage

Assessed measure	Correlation with ISL	Pearson's rho	P-value	Significant (after multiple comparison correction)
thigh subcutaneous tissue thickness	moderate positive	0.27	0.09468776	no
thigh muscle tissue thickness	moderate negative	-0.29	0.07180457	no
thigh subcutaneous thickness fraction	moderate positive	0.38	0.01939431	no
thigh subcutaneous area fraction	moderate positive	0.33	0.04005312	no
leg subcutaneous tissue thickness	strong positive	0.59	7.29E-05	yes
leg muscle tissue thickness	low negative	-0.11	0.51131505	no
leg subcutaneous thickness fraction	strong positive	0.60	4.11E-05	yes
leg subcutaneous area fraction	strong positive	0.61	2.529E-05	yes

Conclusion

- **Leg** subcutaneous thickness, subcutaneous thickness fraction, and subcutaneous area fraction of lower limb strongly correlate with ISL lymphedema stage.
- **Thigh** subcutaneous thickness, subcutaneous thickness fraction, and subcutaneous area fraction of the thigh only **moderately** correlated with ISL stage. This correlates with disease progression.
- The leg subcutaneous thickness fraction is a quick assessment that can be easily reported.

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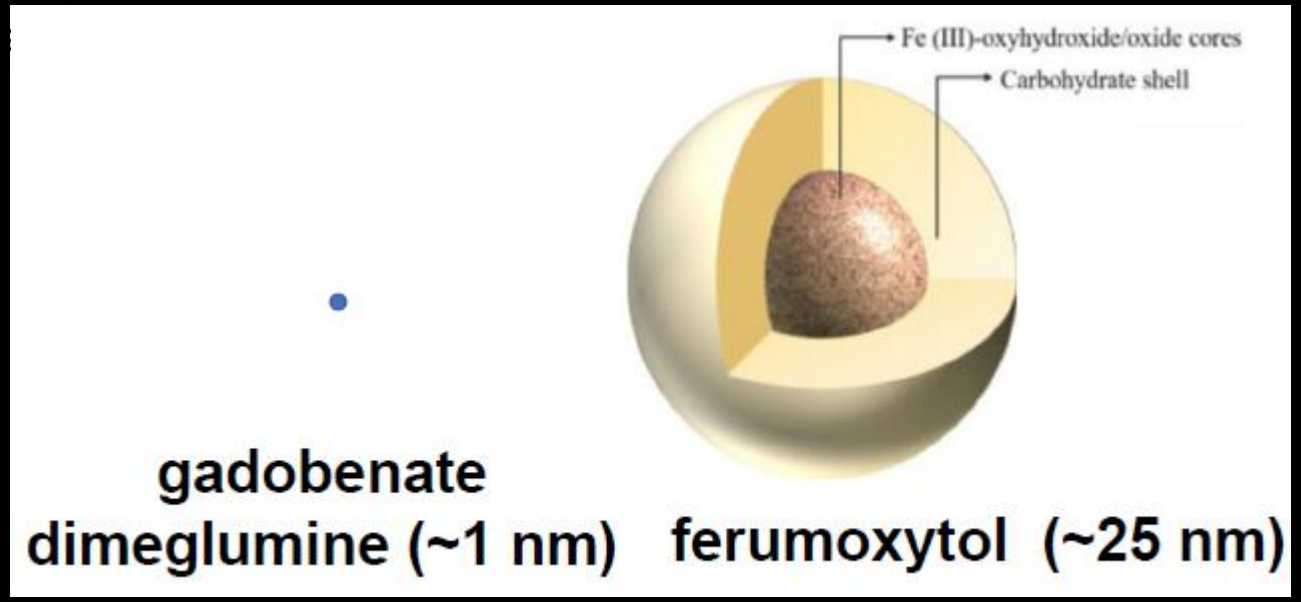
  - Typically, with General Anesthesia
- Gad-MRL
  - Intracutaneous Gad
  - Venous contamination
- DARC MRL(Maki et al 2016)
  - Intracutaneous Gad + IV ferumoxytol
- ION-MRL
  - Intracutaneous ferumoxytol
  - Ideal particle size 17-31 nm
  - Comparable transit time to gad
  - Risk of anaphylaxis (10x Gad)
  - Skin Discoloration



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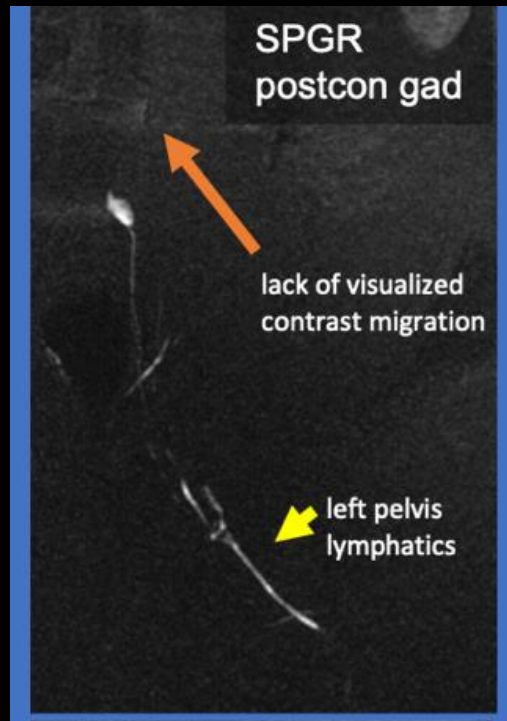
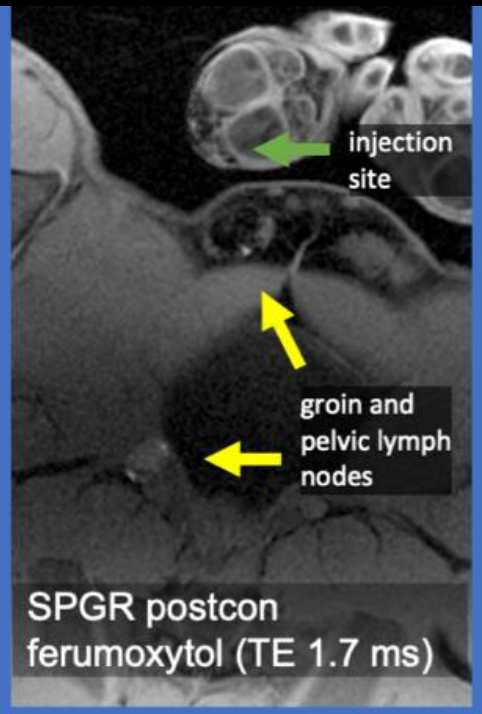
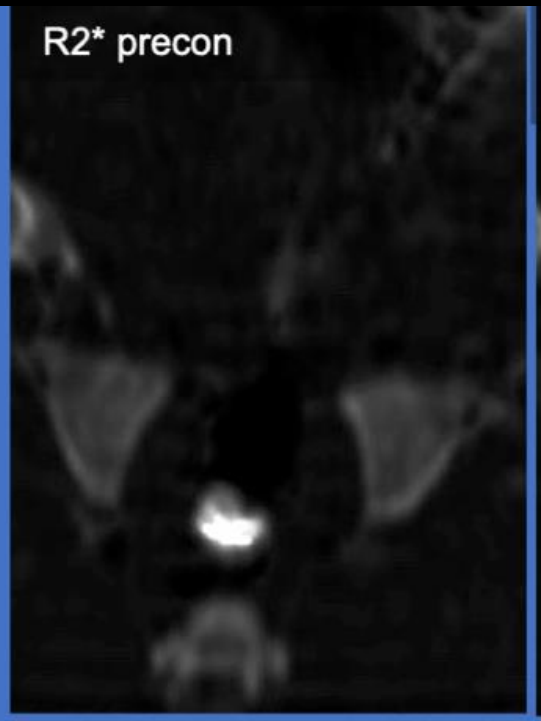
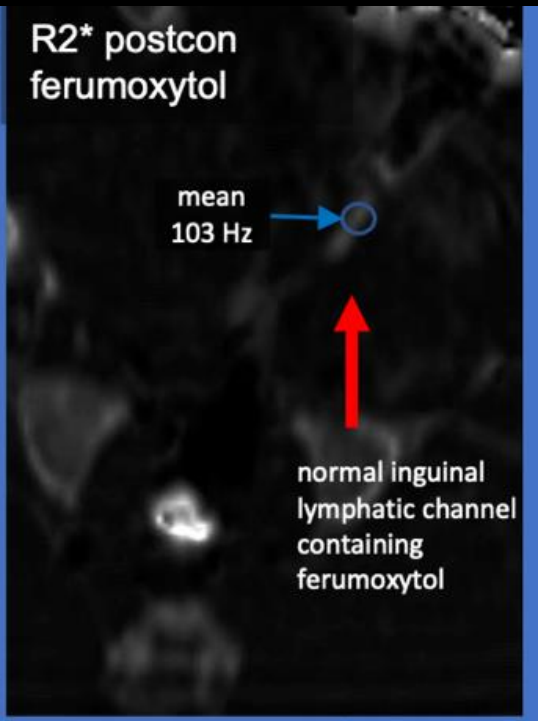
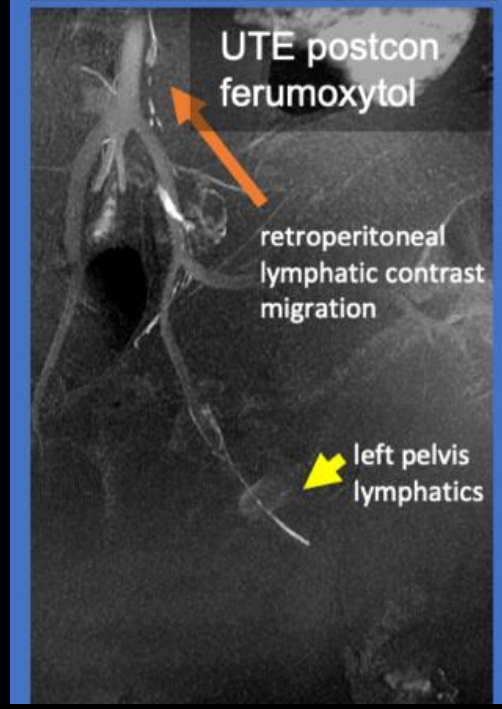
Normal Pig Gad-MRL and ION-MRL

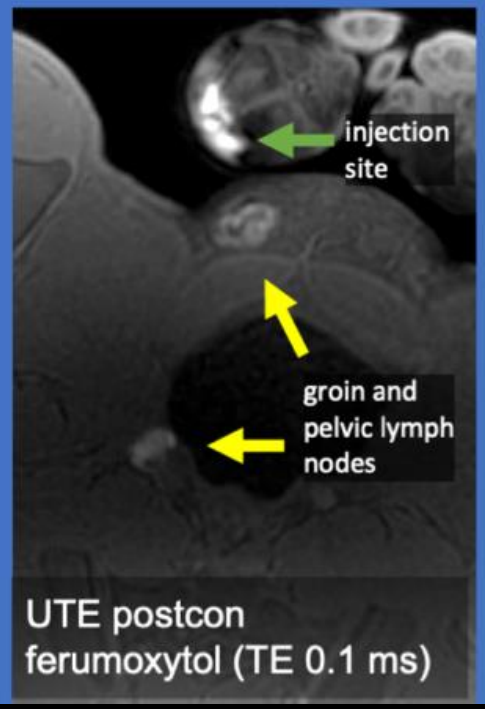


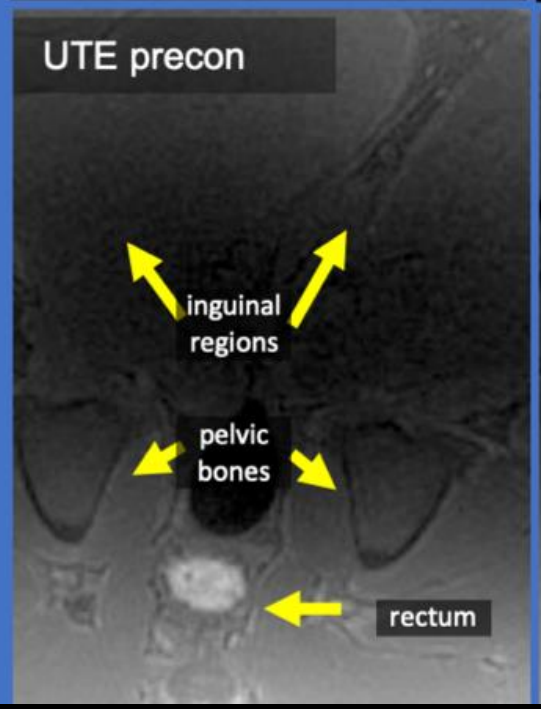


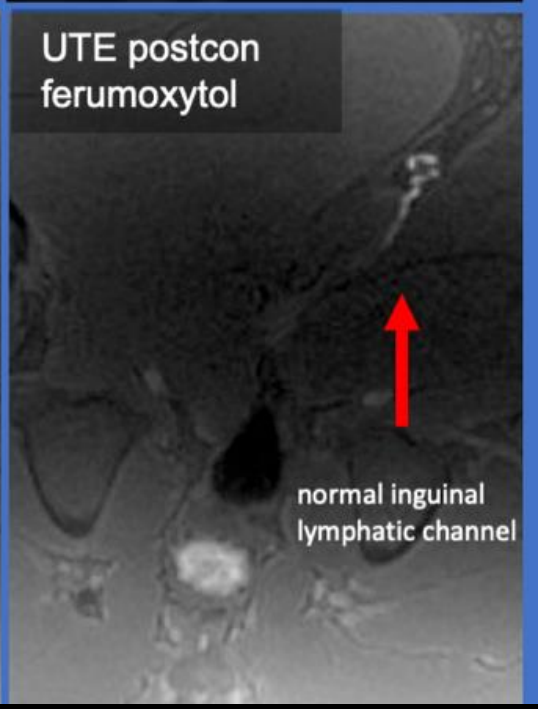






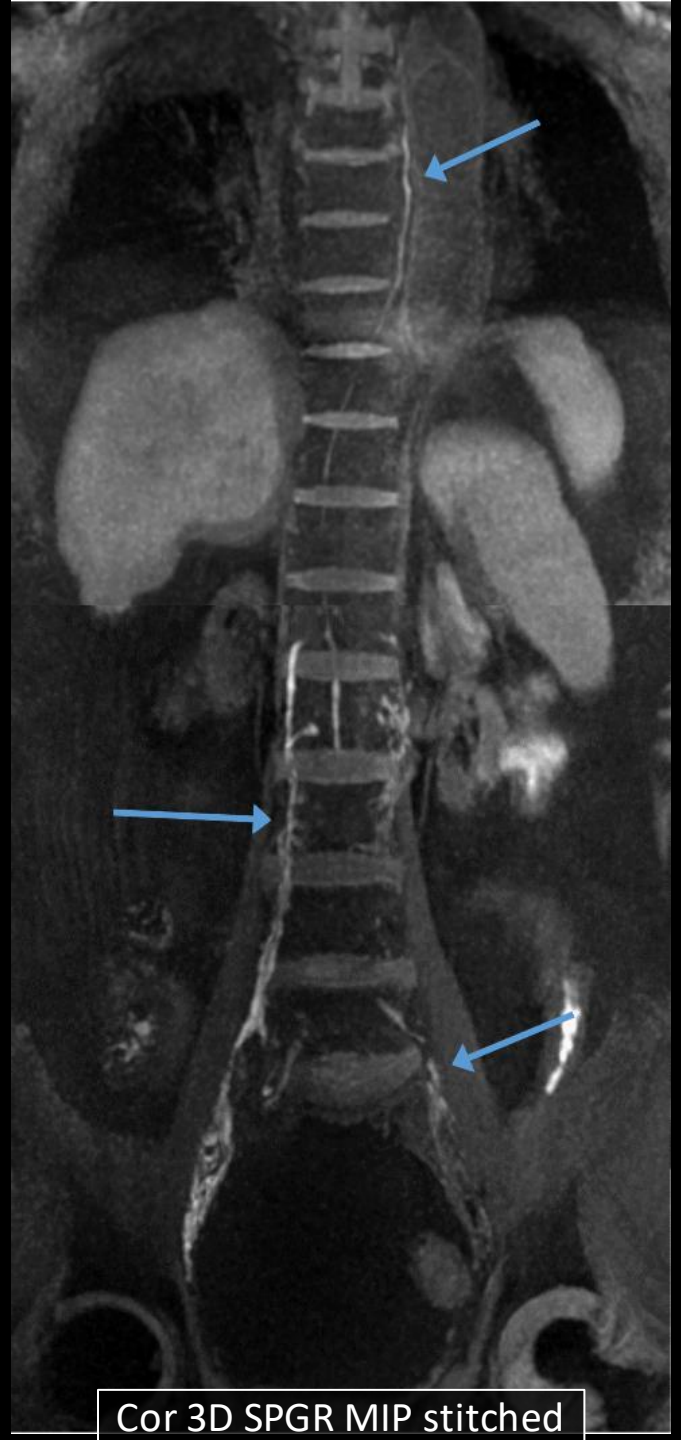






ION-MRL Case 1

- 58 yo M with metastatic gastric cancer status post gastrectomy with chylous ascites
- ION-MRL selected 2/2 renal failure
- ION-MRL demonstrated thoracic duct continuity and no evidence of extravasation



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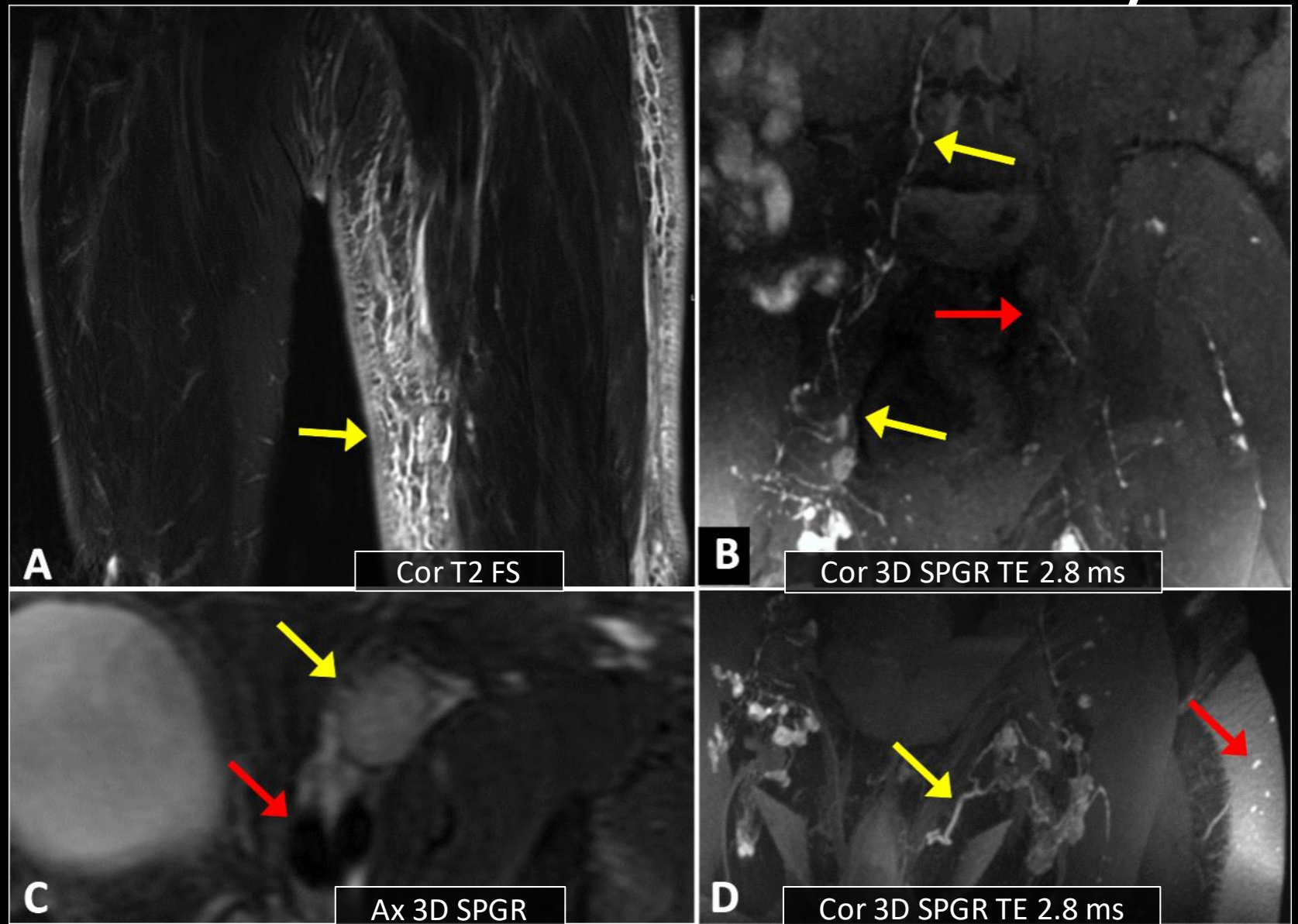
ION-MRL Case 2: 64 yo m with prostate cancer and left lower extremity edema.



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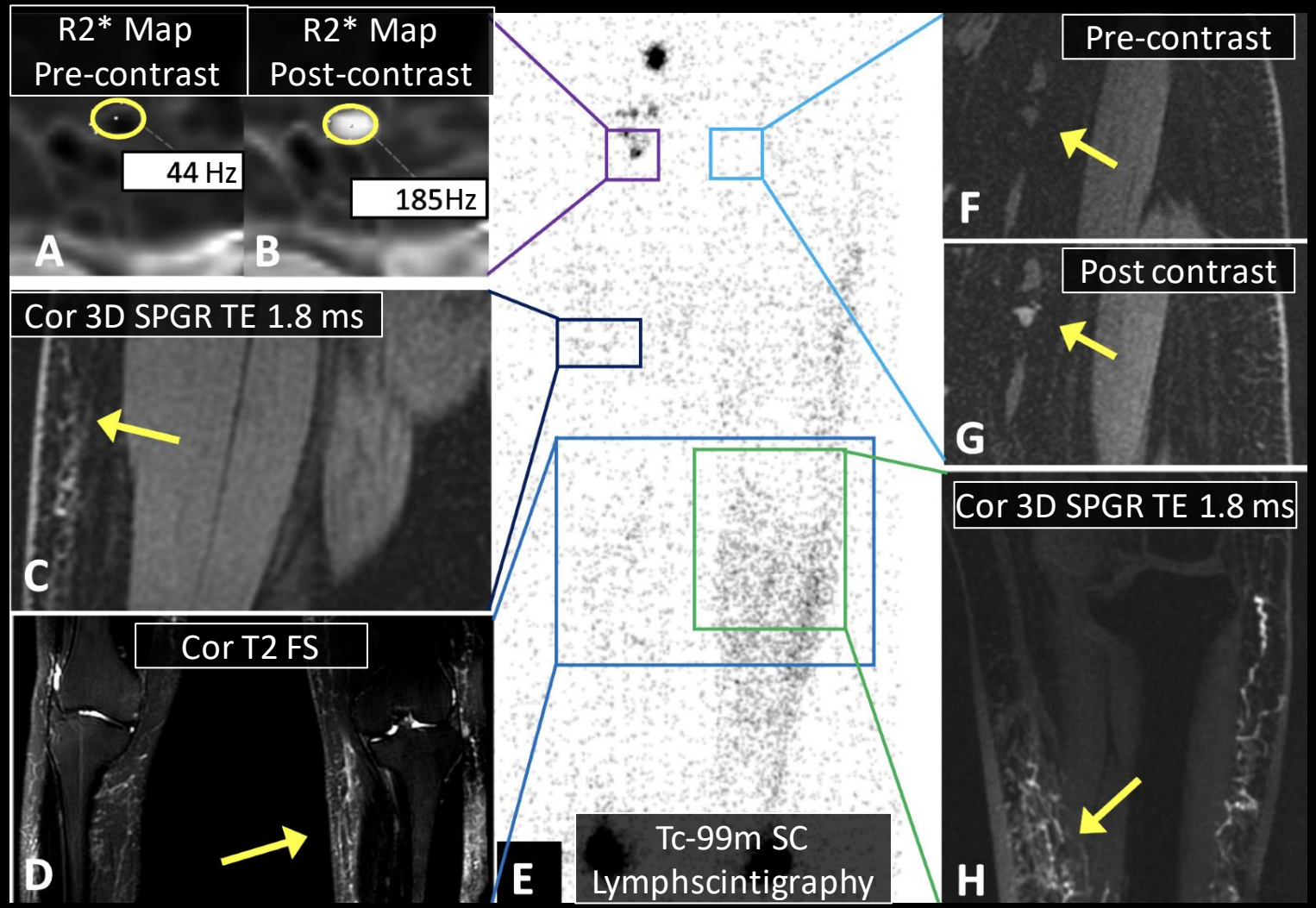
ION-MRL Case 3

- 19-year-old male with protein -losing enteropathy with diffuse edema including the left lower extremity and bilateral hands.



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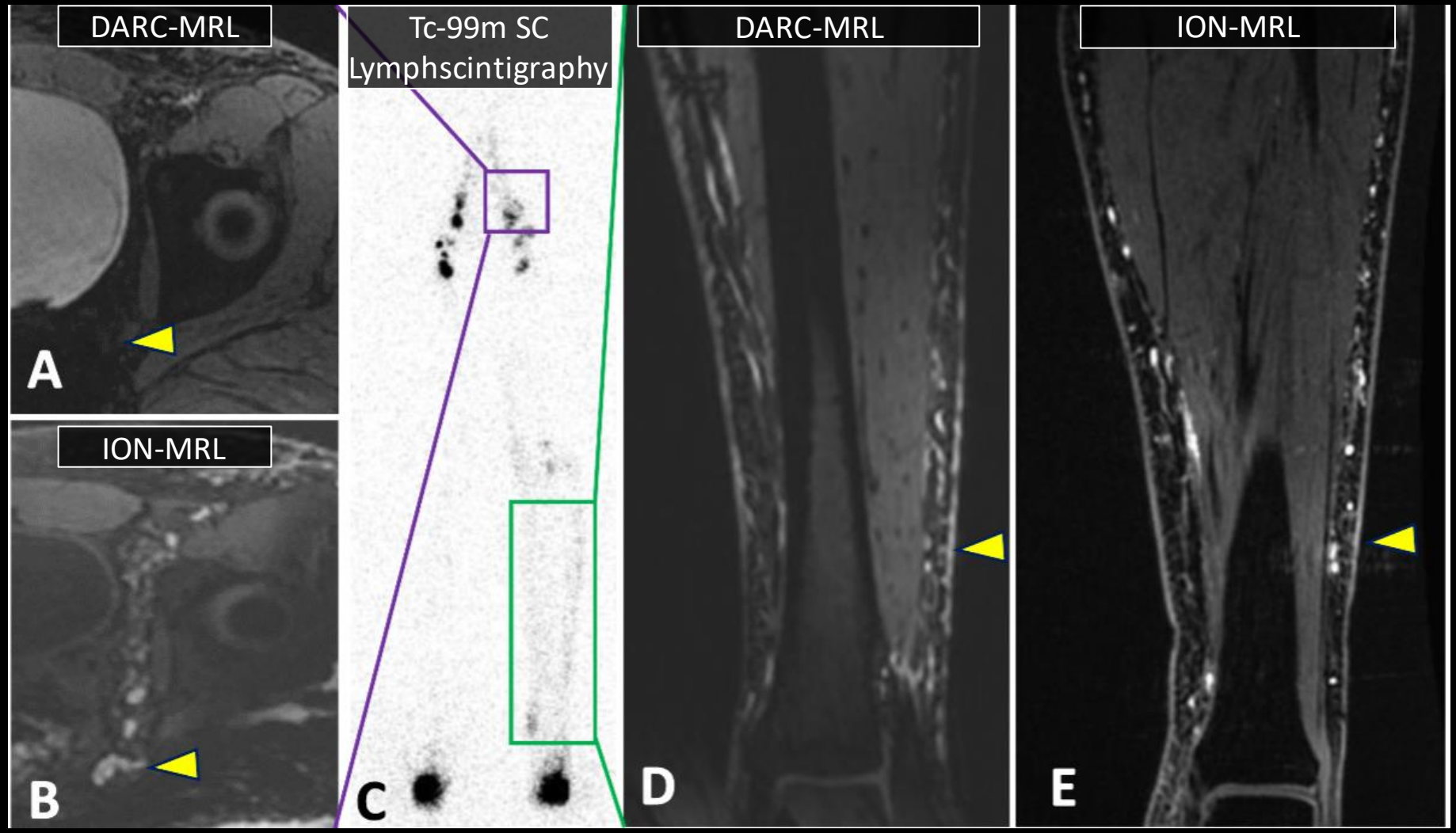
ION-MRL Case 4

- 22-year-old male with left lower extremity edema s/p left iliac stent placement for presumed May-Thurner syndrome now with evaluation for vascularized lymph node transfer.



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ION-MRL Summary

- Contrast remains in the lymphatic system without venous contamination
- Better visualization of the proximal lymphatic system
- No ultrasound guidance or general anesthesia
- Increased risk of adverse reaction
- Skin discoloration for weeks to months
- Dermal backflow is less conspicuous compared to DARC-MRL.

Overview

- Background on Lymphatic Disease and Lymphatic Imaging
- Drug Trial
- MR Lymphangiography
  - DARC-MRL
    - Technique
    - Staging
  - ION-MRL
- Teaser: Novel Treatment for Lymphedema

Stellate ganglion block (SGB)

- **Blocking nerve signals** from the **stellate ganglion** with **local anesthetic** can help to:
  - Reduce **limb volume** in LE

Kim et al. Support Care Cancer. 2015;23(8):2305-2310.

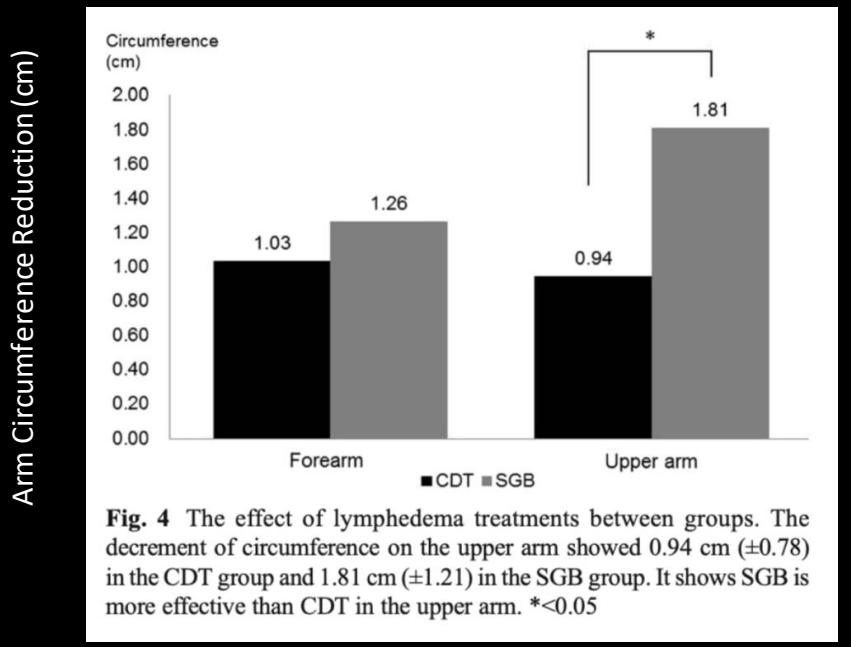

Fig. 4 The effect of lymphedema treatments between groups. The decrement of circumference on the upper arm showed 0.94 cm (±0.78) in the CDT group and 1.81 cm (±1.21) in the SGB group. It shows SGB is more effective than CDT in the upper arm. *<0.05

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Conclusions

- The lymphatic system is poorly understood and implicated in a variety of disease processes
- More funding is becoming available for lymphatic research
- New and emerging therapies are on the horizon
- Clinical need for advanced lymphatic imaging and function quantification
- MRL is a powerful tool but much work remains

Thanks

- T32 CA009695
- Stanford Biodesign Funding


Ali Syed, MD


James Yoon, MD


Bruce Daniel, MD


Sandy Napel, MD


Biodesign Team with Paul Yock, MD and Lyn Denend


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