Quantitative Imaging Biomarkers in Ultrasound Elasticity Imaging

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Proposed Biomarkers

- Shear wave speed for quantifying liver fibrosis
- Shear wave imaging for breast tumor classification
  - Elastic modulus
  - Tumor volume

Outline

- Techniques and potential biomarkers measured
  - Underlying physics
- Degree of fit with QIBA biomarker selection criteria:
  - Transformative
  - Translational
  - Feasible
  - Practical
  - Collaborative
- Numbers of exams that might be involved in the US and worldwide by use of the biomarker
- QUALY's saved, or most important impact estimates that can be made reasonably
- Implementations by the various manufacturers
- Clinical demand

Acknowledgements

- Many thanks to my friends at Duke University
  - Kathy Nightingale
  - Mark Palmeri
  - Gregg Trahey
- Most of the content presented here was developed by them

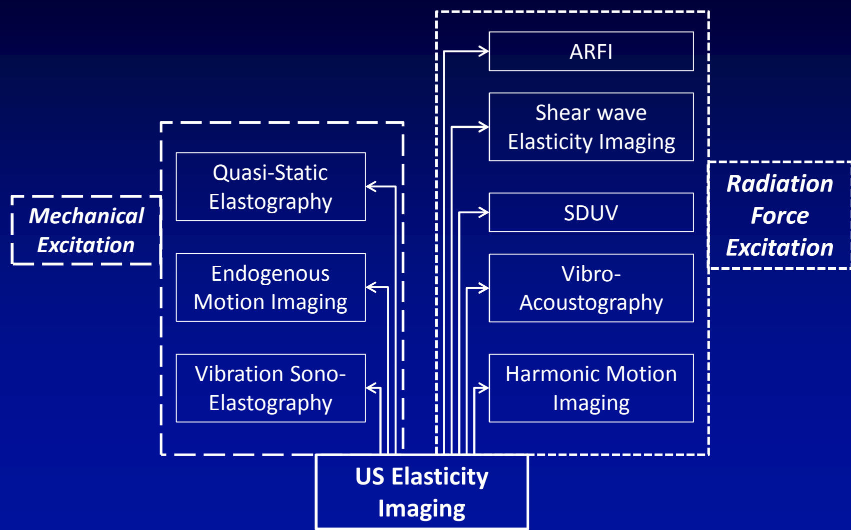
"Elasticity" as a Quantitative Biomarker

- Analogous to the stiffness of a spring
  - How hard do you have to push on it to change its length
    - Relate force on the spring to its stretch or compression
- In 3D we relate force (stress) to displacement (strain)
  - "strain imaging" (relative displacement)
  - Other more sophisticated methods for elasticity imaging
    - Shear wave speed
    - Elastic modulus imaging
    - Nonlinear elasticity imaging

What is "Elasticity Imaging"?

- Two-step process
  - Apply a force
  - Watch what happens
    - Using ultrasound (or MRI, or OCT, or…)
- Categorize imaging approaches by the type of force used to induce displacement

Methods for Elasticity Imaging



"Elasticity" Depends on Rate

Consider a simple thought experiment

- Slowly lower your finger into a pool of water
  - Your finger enters slowly without significant disruption of the surface
  - You feel almost nothing except wet
- Slap the surface of the water with your hand
  - The water splashes
  - It 'hurts' a little
- Fall from the sky into the ocean (say 10,000ft up)
  - The water splashes
  - Contacting the water is not much different than falling on a cement roadway

"Elasticity" Depends on Rate

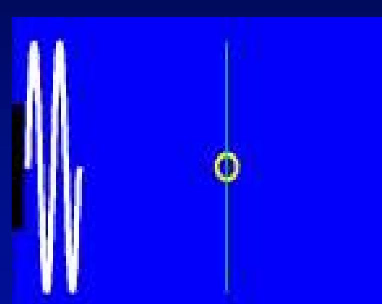
- Absolute "Stiffness" estimated with one system might not equal that obtained with another system
  - The elastic modulus depends on the rate at which force is applied
    - Quasi-static elastography is about 1Hz
    - Radiation force elastography is about 50Hz—1kHz
  - *Use caution when comparing systems*
    - *Expect the modulus estimated with radiation force methods to be higher than that estimated with freehand palpation*

Acoustic Radiation Force

Force generated by a transfer of momentum from an acoustic wave to the medium through which it is propagating, caused by absorption (predominantly) and scattering in soft tissue. Force magnitude typically ~3 g/cm^3

$$F = \frac{2\alpha I_{ta}}{c}$$

α = absorption coefficient
I_{ta} = temporal average intensity
c = speed of sound

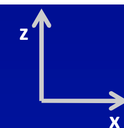


Nyborg, W. *Acoustic Streaming*, in Physical Acoustics Vol. IIB, editor: Mason W.P., Academic Press,1965.

Wave Propagation in Soft Tissues

Transverse (Shear) Wave (1-5 m/s)

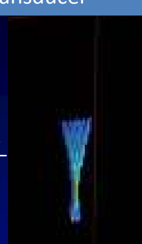
Ultrasound (compression) Wave (1540 m/s)



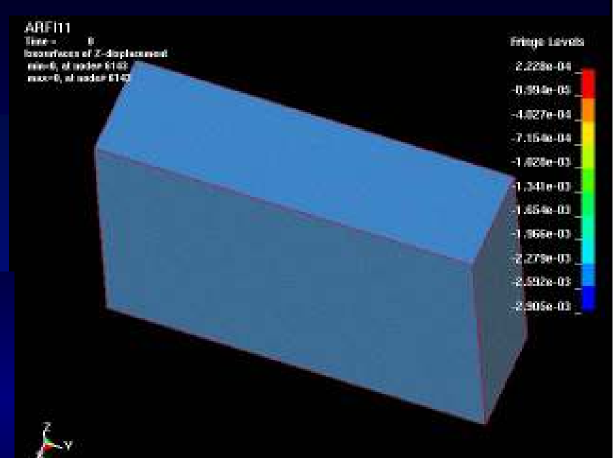
http://www.kettering.edu/%7Edrussell/Demos/waves/wavemotion.html

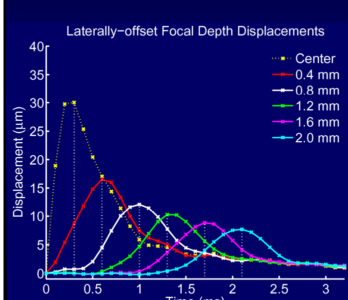
Acoustic Radiation Force

transducer



$$F = \frac{2\alpha I_{ta}}{c}$$

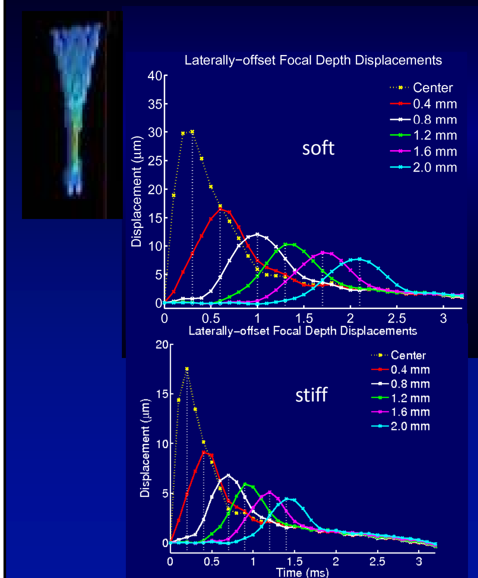


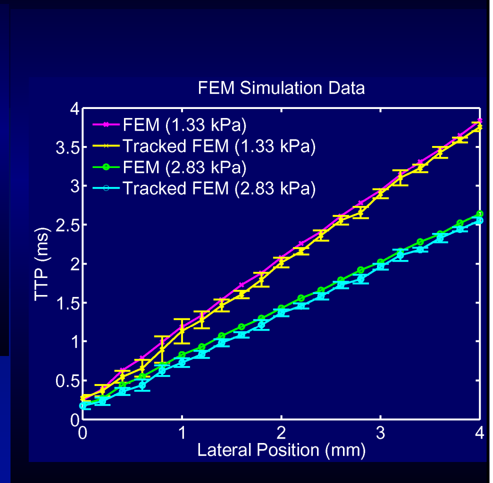


μ=1 kPa, movie duration = 10 ms

Palmeri et , *IEEE UFFC*, 52(10): 1699-1712, 2005.

Estimate shear wave speed with linear regression





C=inverse slope

$\mu=\rho c^2$

Relating material parameters

- Young's modulus: E
- Shear modulus: μ
- Shear wave speed: c_T

$$E = 3\mu = 3\rho(c_T)^2$$

- Linear, isotropic, elastic solid (anistotropy?)
- Incompressible (ν = 0.5), [-1:0.5]
- May be a function of viscosity (dispersive)
- May be a function of strain (nonlinear)
- Poroelastic?

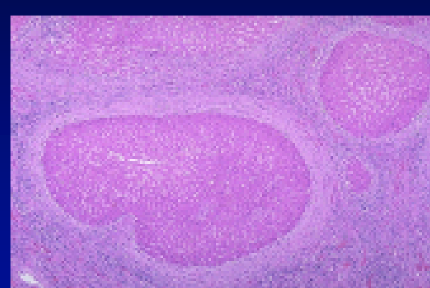
Liver Biopsy

- Diagnostic gold-standard
  - Invasive
    - Infection
    - Hemorrhage
    - Pain
  - Limited sampling
  - Costly (time and money)
  - Not suitable for longitudinal monitoring of disease progression / resolution
- Can a non-invasive liver stiffness estimate be used as a surrogate measure of liver health?

http://www.medandlife.ro/assets/images/Vol%20II%20NO%204/generalarticles/fierbinteanu/image005.jpg

Liver Fibrosis Staging

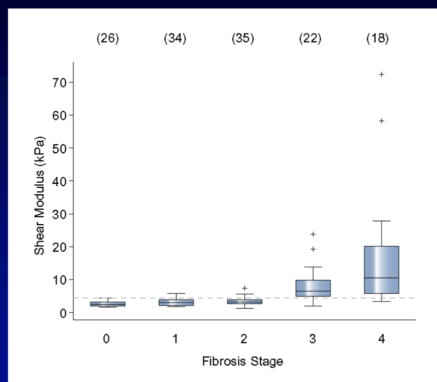
- Stage 0: Normal
- Stage 1: Zone 3 perisinusoidal / periportal
- Stage 2: Perisinusoidal / periportal fibrosis
- Stage 3: Bridging fibrosis
- Stage 4: Cirrhosis



http://homepage.smc.edu/wissmann_paul/anatomy2textbook/liverCirrhosis.jpg

http://www.sciencephoto.com/image/252776/large/M1300676-Cirrhosis_of_the_liver-SPL.jpg

Shear Modulus vs. Fibrosis Stage



- 4.24 kPa F0-2:F3-4 threshold
- 90% sensitivity
- 90% specificity
- 0.90 AUC

Journal of Hepatology **2011** vol. 55 | 666–672

Noninvasive evaluation of hepatic fibrosis using acoustic radiation force-based shear stiffness in patients with nonalcoholic fatty liver disease

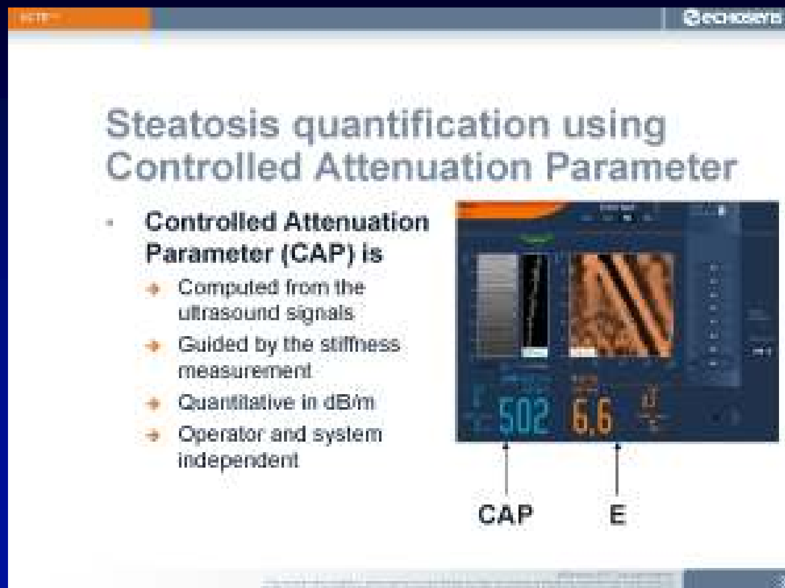
Mark L. Palmeri[1,*], Michael H. Wang[1], Ned C. Rouze[1], Manal F. Abdelmalek[2], Cynthia D. Guy[3], Barry Moser[4], Anna Mae Diehl[2], Kathryn R. Nightingale[1]

[1]*Department of Biomedical Engineering, Duke University, Durham, NC, USA;* [2]*Division of Gastroenterology and Hepatology, Duke University Medical Center, Durham, NC, USA;* [3]*Department of Pathology, Duke University Medical Center, Durham, NC, USA;* [4]*Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC, USA*

FibroScan® (EchoSens)

- Does not use acoustic radiation force
- Uses fixed-frequency mechanical punch at the skin surface
- Ultrasonic tracking of the resultant shear wave from the skin surface
- Not FDA cleared for use in the USA

FibroScan® metrics



Clinical Studies (ARFI Imaging & FibroScan®)

Nonalcoholic Fatty Liver Disease: US-based Acoustic Radiation Force Impulse Elastography[1]

Radiology

Masato Yoneda, MD, PhD
Kaori Suzuki, MD, PhD
Shingo Kato, MD, PhD
Koji Fujita, MD, PhD
Yuichi Nozaki, MD, PhD
Kunihiro Hosono, MD, PhD
Satoru Saito, MD, PhD
Atsushi Nakajima, MD, PhD

radiology.rsna.org • ***Radiology:*** Volume 256: Number 2—August 2010

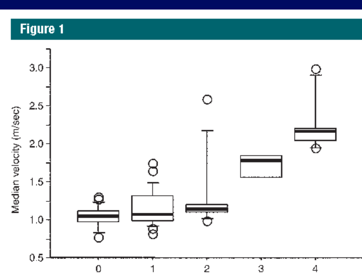


Figure 1: Box plots show interquartile range (box), median (thick line), range (thin lines), and outliers (circles) of median velocity measured by using ARFI sonoelastography. A steady stepwise increase in median velocity was observed with increasing severity of hepatic fibrosis ($P < .0001$, Kruskal-Wallis test).

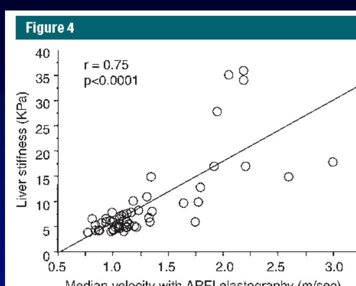


Figure 4: Graph shows correlation between median velocity measured by using ARFI sonoelastography and liver stiffness measured by using transient sonoelastography.

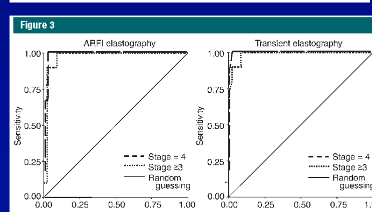
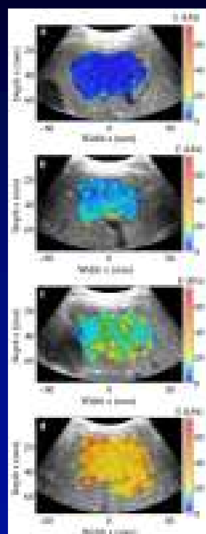
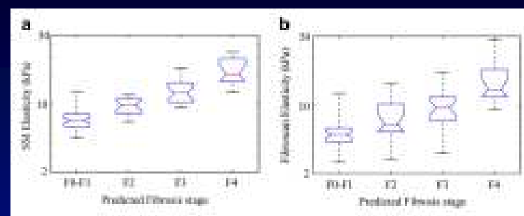
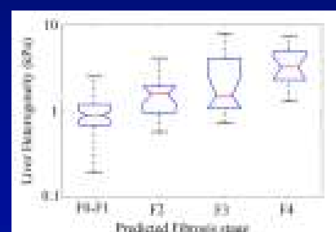


Figure 3: Receiver operating characteristic curves for the entire population of 54 patients.

Supersonic Shear Imaging: Liver Fibrosis





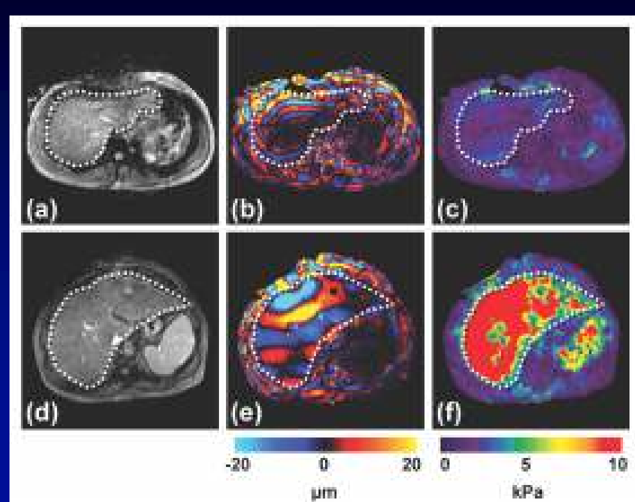


Bavu et al. “Noninvasive In Vivo Liver Fibrosis Evaluation Using Supersonic Shear Imaging: A Clinical Study on 113 Hepatitis C Virus Patients,” UMB, 37(9), 2011.

Magnetic Resonance Elastography

Normal

Cirrhotic



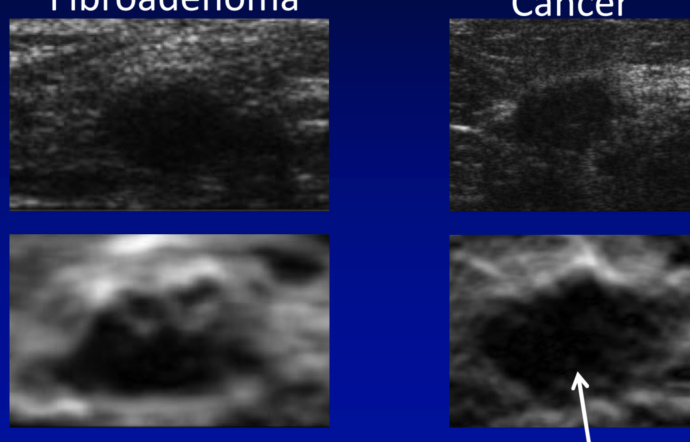
Mariappan, Glaser and Ehman, “Magnetic Resonance Elastography: a review,” Clinical Anatomy, 23, 2010.

Breast Cancer

- 1-in-8 women will develop breast cancer
- > 207,000 new cases of invasive cancer diagnosed in 2010 in the US
- Second leading cause of cancer death in US women
- 70-80% occur in women with no family history
- Risk factors:
  - Aging woman
  - BRCA1 / BRCA2

Breast Lesion Elastograms

Fibroadenoma   Cancer



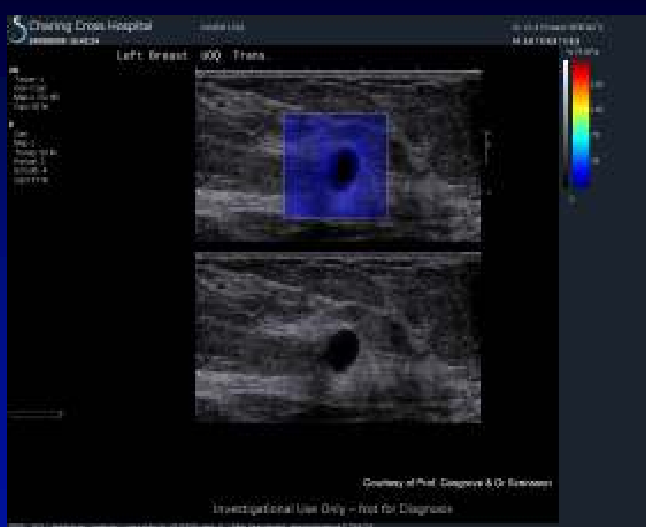
Larger region of decreased strain; desmoplasia?

Supersonic Shear Imaging: Breast Imaging

Dr Balu Maestro, Nice France

- 77 years old
- Previous IDC 6 years ago.
- Recurrence of IDC. Surgery for a 15mm IDC with grade III.
- Sentinel lymph node method.
- This lymph node is considered as suspect.
- N0, no malignant lymph node.
- Emean < 30kPa

Supersonic Shear Imaging: Breast Imaging



Simple cyst.

No ShearWave propagation in liquids.

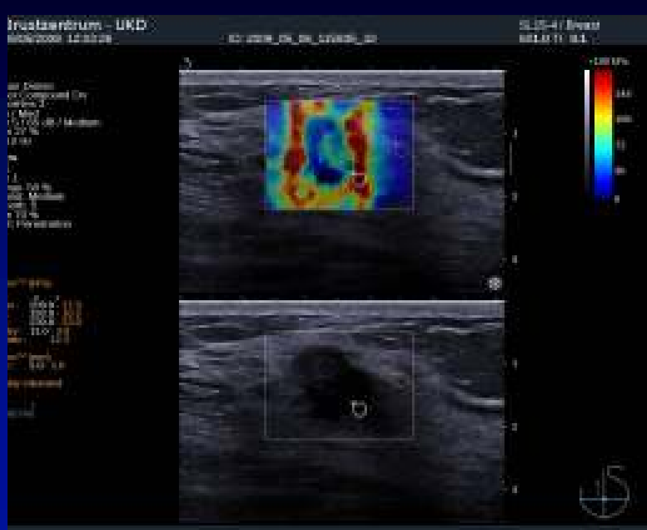
Dr Svensson, London UK

Supersonic Shear Imaging: Breast Imaging

- BIRADS 5 at mammo & US.
- IDC Grade I with necrotic center proved by surgery sample palpation.
- Emax > 200kPa on surrounding tissue
- E = 40kPa in the lesion center

Dr Balu Maestro, Nice France

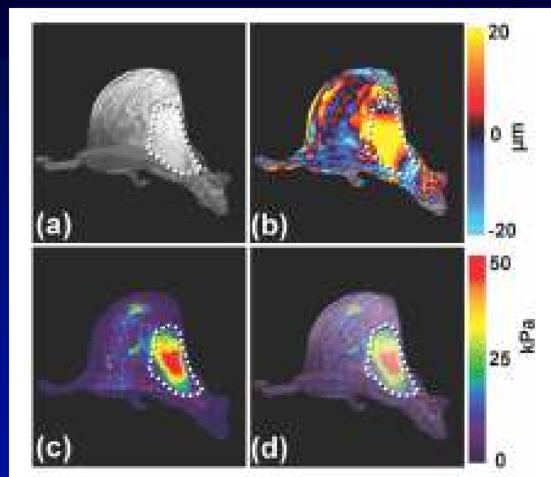
Supersonic Shear Imaging: Breast Imaging



- Invasive Ductal Carcinoma
- T1 (16mm)
- N0
- G2
- HR: +
- HER2: 3+
- 47 years old
- Emean > 200 kPa with lesion/fat stiffness ratio > 12

Courtesy of Dr Nestle-Krämling

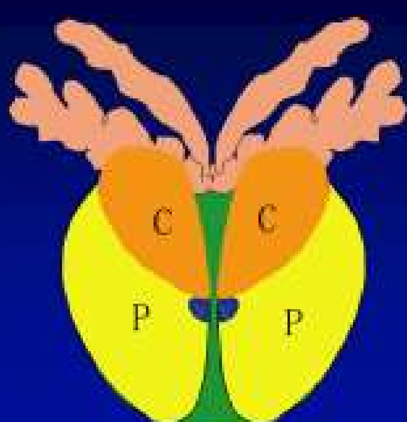
Magnetic Resonance Elastography



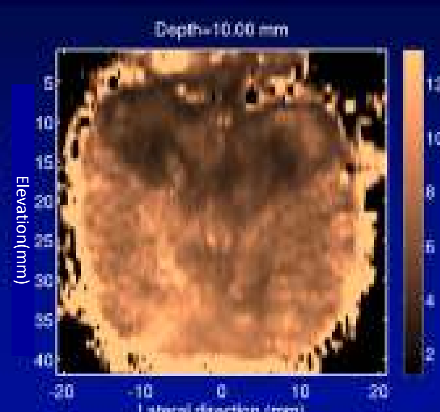
Mariappan, Glaser and Ehman, "Magnetic Resonance Elastography: a review," Clinical Anatomy, 23, 2010.

Ex vivo ARFI prostate images

McNeal Zonal Anatomy *



ARFI Image



*McNeal JE, *The zonal anatomy of the prostate*, Prostate, (1981) 2, 35- 49

Limitations & future directions

- Many assumptions surrounding tissue homogeneity
  - when is isotropy actually appropriate?
- Elastic nonlinearity, viscosity and anisotropy considerations are important
- Disease etiology may play a significant role in tissue stiffness
- Need for large-scale clinical studies and research validation in the quantitative methods
- Reassess the acoustic output limitations for acoustic radiation force imaging modalities

Conclusions

- Potential biomarkers identified
  - Shear wave speed for staging liver fibrosis
  - Breast tumor classification
- Underlying physics reasonably well understood
- Degree of fit with QIBA biomarker selection criteria:
  - Transformative: Likely to change clinical workflow
  - Translational: Laboratory studies and preliminary clinical trials completed
  - Feasible: In clinical use outside of USA
  - Practical: Easy to perform
  - Collaborative: world-wide interest
- Implementations by the various manufacturers
  - At least two ultrasound system manufacturers