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Innovations in Ultrasound & Breast Cancer Imaging

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Disclosure

Mayo Clinic and some investigators have potential financial interests related to the technologies referenced in this presentation.

- **Research Areas: Ultrasound**
  - Vibro-acoustography (VA)
  - Elastography techniques
  - High Resolution Microvasculature imaging and quantification
  - Deep Learning (Automatic segmentation and classification of breast masses)

Breast Imaging

- **X-ray mammography:** Low sensitivity

Limitations:
  - Pregnant women
  - Lactating women
  - Young women with dense breasts
  - High-risk women
- **Conventional Breast Ultrasound-** Low specificity
- **MRI** - High sensitivity

Limitations:
  - Low specificity
  - High cost
  - Less available
- **Need:** Low cost, non-invasive, high specificity imaging tool for breast cancer detection

Advantages of Ultrasound Imaging

Advantages:
Non-ionizing
Real-time
Large imaging depth
Cost-effective
Portable and widely available

Ultrasound is the most widely used imaging modality in clinical practice

Ultrasound Technology Trends

Seeking new information

- Acoustic imaging
- Ultrasound elastography techniques
- Contrast-enhanced imaging
- Ultrafast Doppler microvasculature imaging

Vibro-acoustography (VA) in Breast Cancer Detection

Imaging and estimation of tissue stiffness

VA and ultrasound elastography techniques: palpation like information

VA: New Breast Imaging Methodology

•Tissue stiffness is closely related to pathology of tissue.

Goal: To develop a new high-resolution imaging method that is sensitive to tissue stiffness.

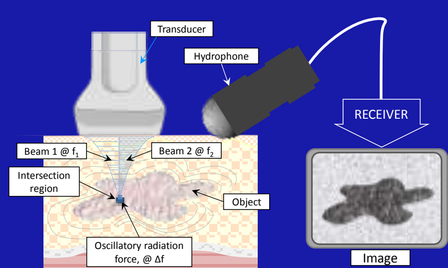
Approach: Use Vibro-acoustography (VA) for breast imaging

Principles of Vibro-acoustography

Concept: Vibro-acoustography uses Radiation force of US to produce images at low frequencies

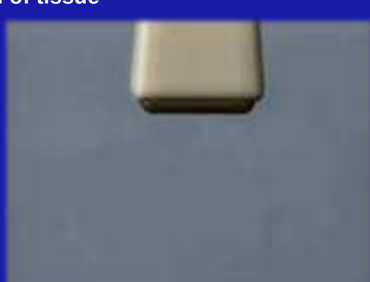
Main steps in vibro-acoustography:

1. Vibrate object by "*radiation force*" of ultrasound
2. Record the sound from object response
3. Image object by scanning



Vibro-acoustography

Sound of tissue

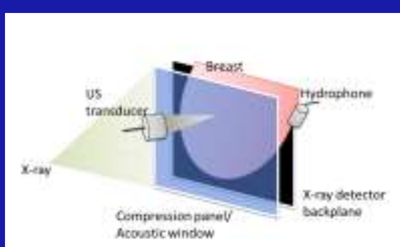


In Vivo Breast Applications of VA

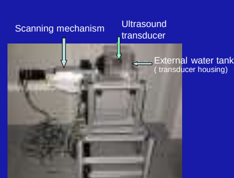
Objective:
- Evaluate the Performance of VA in differentiation of breast masses

Description of Study Cohort:
- 60 patients with suspicious breast lesions
  Age>18 years

System Used:
Integrated mammography ultrasound system (Vivid 7 GE)



Combined Vibro-acoustography-Mammography System



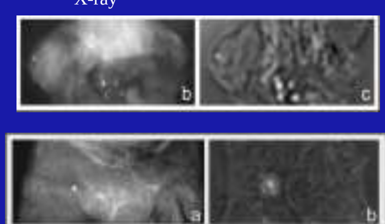
VA Scanner

Main Features of VA

VA image features	Implications
• Provides new information not available from sonography • Sensitive to stiffness. • Speckle-free • Sensitive to calcification • High contrast images	More Diagnostic Information

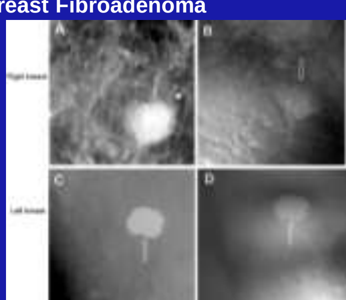
X-ray

Vibro-acoustography



Examples of Breast VA

Breast Fibroadenoma



71 years old woman

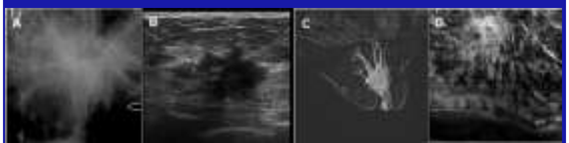
Right breast Mammography:2 cm, sharply marginated mass with coarse lobulation

Left breast Mammography: calcified mass

Alizad et. al., *Breast Cancer Research* , 2012.

Examples of Breast VA

Infiltrating lobular carcinoma, GII



67 years old woman
Mammography : Spiculated mass
US: Hypoechoic mass with irregular border

Alizad et. al., *Breast Cancer Research* , 2012.

Examples of Breast VA

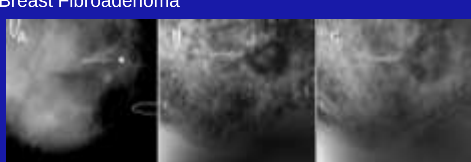
Invasive ductal carcinoma G. II

64 years old woman
Mammography : Minimal architectural distortion, increased soft-tissue density
US: 5 × 7 mm hypoechoic lesion with posterior shadowing
VA: mass with higher contrast fine spiculations

Alizad et. al., *Breast Cancer Research* , 2012.

Examples of Breast VA

Breast Fibroadenoma



42 year old woman with palpable abnormality
Mammography: dense but unremarkable
VA: Round mass with defined border and some lobulations

Diagnostic accuracy :
Sensitivity (95% CI), % 80
Specificity (95% CI), % 94

Alizad et. al., *Breast Cancer Research* , 2012.

Breast VA: Concluding Remarks

Diagnostic accuracy
Sensitivity (95% CI), % 80
Specificity (95% CI), % 94

- VA can be used breast cancer diagnostic tool as a complementary to conventional US
- VA is sensitive to tissue stiffness, detect MCs, a sensitive tool for early diagnosis and in patients with dense breast where mammography fails
- Future work is to improve handheld VA for a clinical utility

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High Resolution Microvasculature Imaging and Quantification

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Angiogenesis

Understanding the Microvasculature differences in Malignant and Benign Masses

Angiogenesis:

Growth of New Blood Vessels

Normal

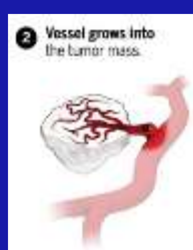
- First vessels in the developing embryo
- Vital process in **growth/ development**
- **Wound healing**

Abnormal

- Tumor vessels lack protective mechanisms
- Lack functional perivascular cells
- Sometimes lack endothelial cells in vessel wall
- Transition of tumors from a benign to a malignant state.

Tumor Angiogenesis

- Toward and within tumor
- Starts in tumor as small as 2-4 mm



Role of Microvasculature in Breast Cancer

- **Breast** tumor growth and metastasis are dependent to tumor angiogenesis
- Extent of angiogenesis can be used as **prognostic factor**

Statistically significant correlation of microvessel **density with tumor grade**

Role of Microvasculature Morphology in Malignant/Benign masses

- MVD alone not always a good marker for benign and malignant

Need: To quantify other morphological parameters

- Vessel tortuosity
  - Benign: Straight and regular vessels
  - Malignant: tortuous and irregular vessels
- Vessel diameter
- Number of vessel segments

- ***Imaging and quantification microvascular architecture could be used for breast tumor differentiation***

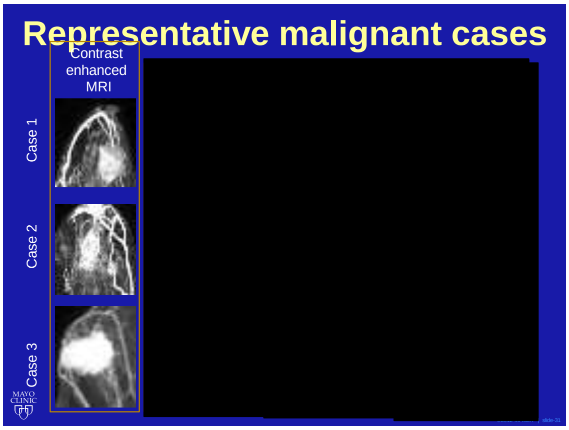
Method: Non-invasive Imaging of Microvessels

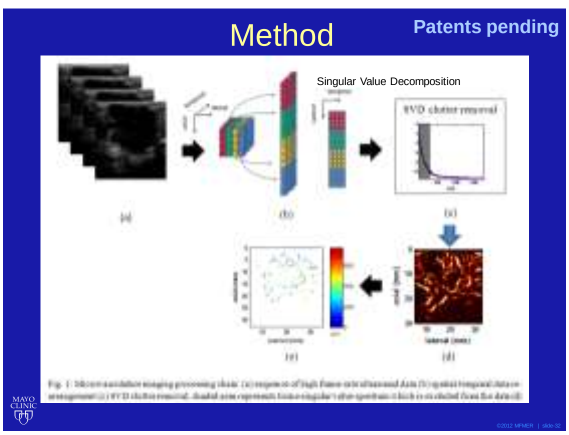
- Conventional US Doppler can only display large vessels
- Value of US Doppler in differentiation of breast masses is limited
- ✓ *Need: Develop new non-invasive tools to provide quantitative information about microvessels of the breast lesion*

Breast Microvasculature Imaging and Quantification

- **Hypothesis**: Microvasculature of breast masses changes with pathology
- **Goal**: Differentiation of breast masses based on microvasculature morphology analysis

Method:
- Ultrafast ultrasound imaging of micro-vessels
- Quantification of microvasculature architecture
- Use the quantified of morphological parameters of microvasculature for differentiation

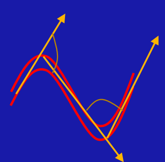

Representative malignant cases
Contrast enhanced MRI
Case 1
Case 2
Case 3


Method
Patents pending
Singular Value Decomposition
SVD clutter removal


Method
Patent Pending

Vessel Tortuosity Metrics

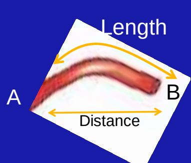
Sum of Angles Metric = SOAM

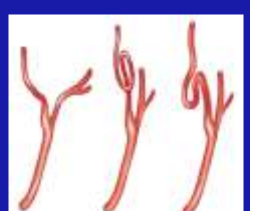


SOAM = Sum (all angles) / Vessel length

Vessel Tortuosity Metrics

Distance metric (DM)





DM = Vessel Length/Distance

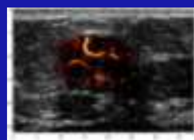
Fibroadenoma. Focal atypical ductal hyperplasia. Fibrocystic changes

Morphological Parameters	
# of vessel segments	30
# of branch points	15
Mean(Diameter)	435

Invasive/Infiltrating Ductal Carcinoma (IDC) Grade III

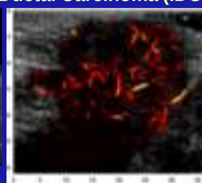
Morphological Parameters	
# of vessel segments	91
# of branch points	47
Mean(Diameter)	637

Fibroadenoma



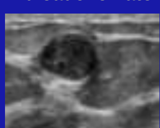
Morphological Parameters	
# of vessel segments	20
# of branch points	11
Mean(Diameter)	394

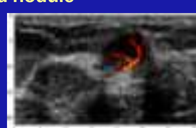
Invasive/Infiltrating Ductal Carcinoma (IDC) G-III



Morphological Parameters	5mm
# of vessel segments	154
# of branch points	102
Mean(Diameter)	474

Fibroadenomatoid nodule





Morphological Parameters	
# of vessel segments	10
# of branch points	6
Mean(Diameter)	463

Metastatic renal cell carcinoma

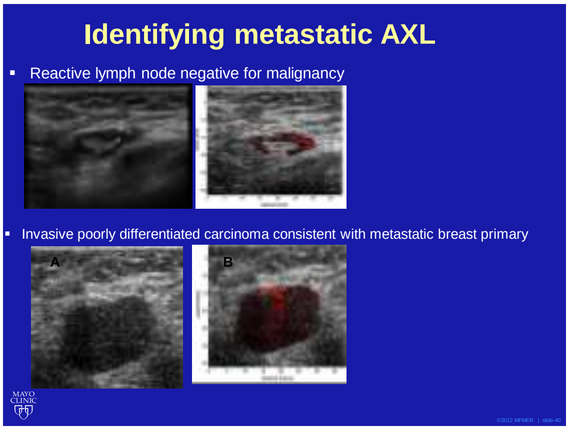
Morphological Parameters	
# of vessel segments	52
# of branch points	40
Mean(Diameter)	393

Fibroadenoma

Morphological Parameters	
# of vessel segments	16
# of branch points	7
Mean(Diameter)	416

Pathology: Invasive ductal carcinoma, grade II.

Lesion Dilation / Parameter	
# of vessel segments	58
# of branch points	38
Mean(Diameter)	451


Identifying metastatic AXL
Reactive lymph node negative for malignancy
Invasive poorly differentiated carcinoma consistent with metastatic breast primary
A
B
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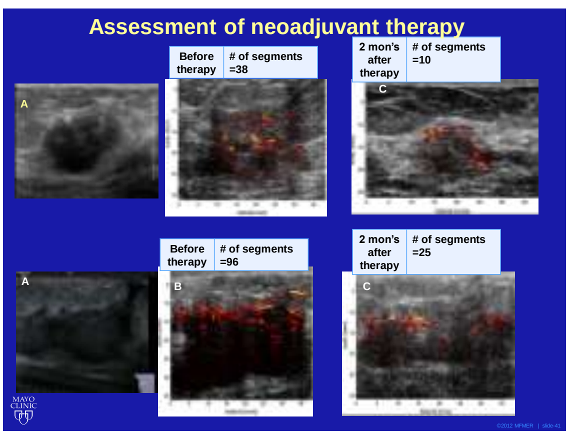
Assessment of neoadjuvant therapy
Before therapy
# of segments =38
2 mon's after therapy
# of segments =10
A
C
Before therapy
# of segments =96
2 mon's after therapy
# of segments =25
A
B
C
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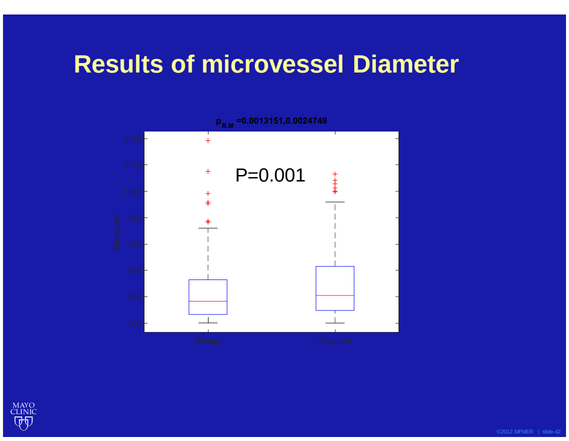
Results of microvessel Diameter
P=0.001
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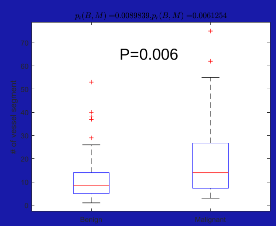
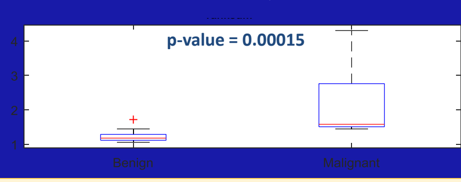
Number of Vessel segments



Benign: 57
Malignant: 40

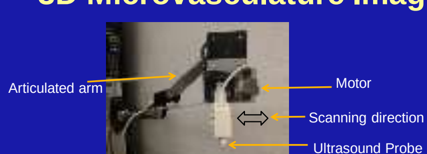
Differentiation of Breast Lesion Using Microvasculature Biomarker

Biomarker: Vessel Tortuosity - Distance Metric



***Conclusion*: Breast masses may be differentiated using microvasculature quantification**

Future Direction: 3D Microvasculature Imaging



Flow phantom: 4 Vessels
2D View
3D vessel views

Summary

- **Introducing a high resolution ultrasound imaging of microvasculature**
- Novelty:
  - Significant clutter reduction: Visualized microvasculature structure with high resolution 300-200µ
  - No contrast enhanced agents
  - Quantified morphology of microvasculature architecture
  - First validation on pre-biopsy breast patients
  - Will use 3D microvasculature imaging for better quantification
  - Prediction of ALN metastasis in breast cancer patients
  - Assessment of neoadjuvant therapy
- Can extended to other organs involving soft tissues

Acknowledgements

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Funding Sources:

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- **R01CA148994**
- **R01CA168575**
- **R21CA121579**
- **R01CA127235**
- **BCTR0504550 (Komen for the Cure)**

Acknowledgements

Thank you!

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Acoustic Radiation Force Elastography Techniques

- Vibro-acoustography (Sound of tissue)
- Acoustic Radiation Force Impulse (ARFI) Imaging
- Shear Wave Elastography:
  - Supersonic Imaging
  - Virtual Touch IQ SWE
  - CUSE
  - Shear Wave Dispersion Ultrasound Elastography

Shear wave Elastography

Shear wave Elastography

- Elastography is a technique to measure the stiffness of tissues.
- ***Tumor stiffening***
  - Collagen crosslinking
  - ECM stiffening
  - Increased focal adhesion

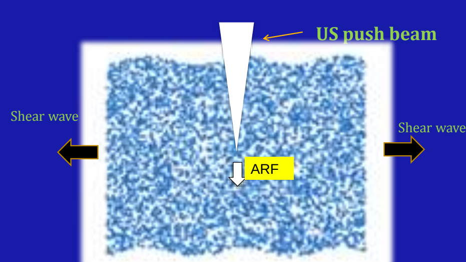
Levental et. al. *Cell*. 2009 November 25; 139(5): 891–906

Elastography

- Elasticity imaging modalities
  - Magnetic Resonance Elastography (MRE)
  - Static Elastography
  - Acoustic radiation Force Impulse (ARFI)
  - Supersonic Imagine (SSI)
  - VTIQ
  - Comb-Push Ultrasound Shear Elastography (CUSE)

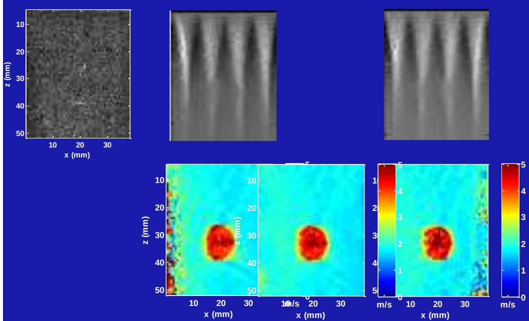
Each technique has certain limitations.

Shear Wave Elasticity Imaging (SWEI)



Elasticity ~ (Shear wave speed)^2

Principles of CUSE[1,2]



[1]Song, et. al., IEEE Trans. On Medical Imaging, 2012
[2]Song, P., et al., IEEE Trans Med Imaging. 2013 Aug;32(8):1435-47.

Breast Shear wave Elastography (CUSE)

Objectives

To investigate the feasibility and performance of a new ultrasound-based shear elastography, **comb-push ultrasound shear elastography**, to measure elasticity in breast masses.

Fund: Grant R01 CA148994(NIH)

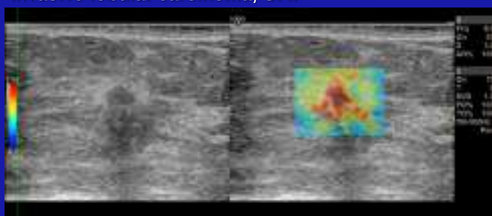
Materials and Methods

Description of Study Cohort:

- 227 patients with suspicious breast lesions
  - Scheduled for biopsy
  - Age range from 18 years and older
- Exclusion criteria:
  - Women with breast implants
  - Women who had mastectomies
- Ultrasound scanner
  - Verasonics investigational ultrasound platform
  - GE Logiq E 9

Results: Review of Selected Cases

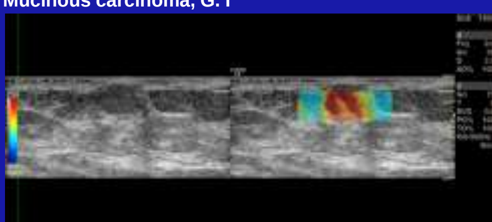
Invasive lobular carcinoma, G. II



66 years old, BIRAD 4,
10 x 7 x 8 mm hypoechoic mass with a hyperechoic rim and angular margins
SWE: high elasticity value E_{mean}=145kPa

Results: Review of Selected Cases

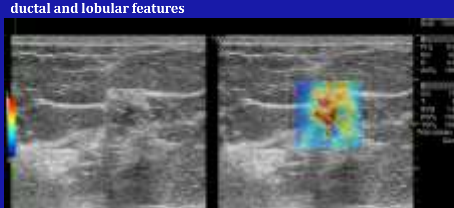
Mucinous carcinoma, G. I



79 years old with palpable abnormality in left breast
US:12 x 9 mm oval circumscribed mass as shown
SWE: high elasticity value with E_{mean}=132.7kPa.

Results: Review of Selected Cases

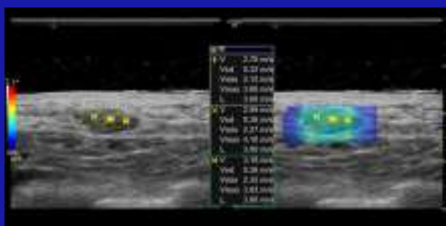
Invasive mammary carcinoma with mixed ductal and lobular features



72 years old, BI-RADS 4
US:13 mm irregular region with posterior shadowing
SWE: Elasticity value E_{mean}=97.7kPa

Results: Review of Selected Cases

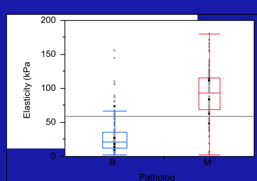
Benign Fibroadenoma



45 years old, palpable abnormality
US; hypoechoic mass
SWE: Elasticity Value E_{mean}=26.7kPa

SWE–LE9 Breast Results

Box plot:

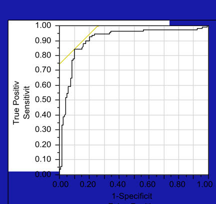


Pathology	Number	Mean (kPa)	Std. Dev. (kPa)	p-value
Benign (B)	119	30.18	27.81	<0.0001*
Malignant (M)	108	90.66	35.55	

SWE–LE9 Breast Results

ROC Analysis

- 227 patients
- Cutoff: 62kPa
- AUC: 91%
- Sensitivity: 84%
- Specificity: 90%
- PPV: 88%
- NPV: 86%



Conclusion

- Specificity: 90% and sensitivity: 84%
- Small malignant case tend to be softer (FN) (apparently or naturally)
- False positives: Benign breast features with High Elasticity value
  - diabetic mastopathy, post operative scar, sclerosis and presence of calcification
- Potential clinical utility
  - CUSE as Quantitative and diagnostic tool complementary to B-mode ultrasound for differentiating malignant and benign breast lesions

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