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
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
Main Features of VA

**VA image features**
- Provides new information not available from sonography
- Sensitive to stiffness
- Speckle-free
- Sensitive to calcification
- High contrast images

**Implications**
- More diagnostic information

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

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

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
Breast VA: Concluding Remarks

- VA can be used as a 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.

High Resolution Microvasculature Imaging and Quantification

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 masses
- 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

Method

Patents pending
SOAM = Sum (all angles) / Vessel length

Vessel Tortuosity Metrics

Sum of Angles Metric = SOAM

Distance metric (DM)

DM = Vessel Length/Distance

Fibroadenoma. Focal atypical ductal hyperplasia. Fibrocystic changes

Invasive/Infiltrating Ductal Carcinoma (IDC) Grade III

Morphological Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
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<tr>
<td># of vessel segments</td>
<td>30</td>
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<tr>
<td># of branch points</td>
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<td>Mean(Diameter)</td>
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Morphological Parameters

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Fibroadenoma

**Morphological Parameters**

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<td># of branch points</td>
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<td>Mean(Diameter)</td>
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Invasive/Infiltrating Ductal Carcinoma (IDC) G-III

**Morphological Parameters**

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<td># of branch points</td>
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Fibroadenomatoid nodule

**Morphological Parameters**

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<td>Mean(Diameter)</td>
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Metastatic renal cell carcinoma

**Morphological Parameters**

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<td>Mean(Diameter)</td>
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Fibroadenoma

**Pathology:** Invasive ductal carcinoma, grade II.

**Lesion Dilatation / Parameter**

<table>
<thead>
<tr>
<th># of vessel segments</th>
<th>58</th>
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<tr>
<td># of branch points</td>
<td>26</td>
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<tr>
<td>Mean(Diameter)</td>
<td>416</td>
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</table>
Identifying metastatic AXL

- Reactive lymph node negative for malignancy
- Invasive poorly differentiated carcinoma consistent with metastatic breast primary

Assessment of neoadjuvant therapy

<table>
<thead>
<tr>
<th>Before therapy</th>
<th># of segments ≤50</th>
<th>2 mons after therapy</th>
<th># of segments ≤10</th>
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<td>A</td>
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</tr>
<tr>
<td>B</td>
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<td></td>
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<tr>
<td>C</td>
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<tr>
<td>C</td>
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Results of microvessel Diameter

P = 0.001
Number of Vessel segments

![Graph showing number of vessel segments for benign and malignant lesions with a p-value of 0.006.]

Benign: 57
Malignant: 40

Differentiation of Breast Lesion Using Microvasculature Biomarker

Biomarker: Vessel Tortuosity - Distance Metric

p-value = 0.00015

Conclusion: Breast masses may be differentiated using microvasculature quantification

Future Direction: 3D Microvasculature Imaging

Articulated arm
Motor
Scanning direction
Ultrasound Probe
Flow phantom
3D View
3D vessel views
Summary

- Introducing a high resolution ultrasound imaging of microvasculature

- Novelty:
  - Significant clutter reduction: Visualized microvasculature structure with high resolution 300-200 μm
  - 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

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- R. Nayak, PhD
- A. Gregory, PhD student
- J. Webb, MS
- S. Adabi, PhD
- P. Lee, PhD student
- N. Bulegato, Grad student
- M. Lattanzi, Grad student
- S. Bae, PhD student

Lab Members:
Thank you!
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

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
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 $E_{\text{mean}}=145\text{kPa}$

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 $E_{\text{mean}}=132.7\text{kPa}$

Results: Review of Selected Cases

Invasive mammary carcinoma with mixed ductal and lobular features

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

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