QUANTITATIVE
SUBHARMONIC IMAGING AND
PRESSURE ESTIMATION IN VIVO

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Disclosures

- GE Advisory Board
- GE Speaker’s Bureau
- Equipment loan from GE Medical
- Contrast agents from GE Healthcare
- Toshiba Speaker’s Bureau
- Equipment loan from Toshiba
- Equipment loan from Siemens
- Contrast agent from Lantheus
Subharmonic Ultrasound Imaging (SHI)

- 3 Stages of subharmonic signal generation:
  - Occurrence
  - Growth
  - Saturation
Implementation: 3D/4D Linear Array

**4D10L broad bandwidth array**
- 3.5 – 11 MHz bandwidth
- 50 x 58 mm footprint
- 37.4 mm x 29º volume

Experimental software implemented on a Logiq 9 scanner (GE, Milwaukee, WI) provided:

- Three-dimensional pulse inversion HI transmitting 2 cycle pulses at 5.0 MHz and receiving at 10 MHz by equalization filtering (peak MI = 0.36)

- Three-dimensional pulse inversion SHI transmitting 4 cycle pulses at 5.8 MHz and receiving at 2.9 MHz by equalization filtering (peak MI = 0.33)

[Eisenbrey et al., Acad Radiol, 2012]
4D SHI Breast Imaging Trial

- Clinical trial of women using 3D HI and 3D SHI to characterize breast masses identified by mammography

- IRB and FDA approved (IND no 112,241)

- Ultrasound contrast agent (UCA) used was Definity (Lantheus Medical Imaging, N Billerica, MA, USA)

- Subjects receive baseline grayscale and power Doppler imaging followed by 3D HI (0.25 ml) and 3D SHI (20 µl/kg) exams prior to biopsy
Example Case:

56 year old woman with 23x9 mm lesion identified by mammography and scheduled for biopsy
Example Case:
Example Case:

Fragment of Intraductal Papilloma

3D SHI
Identifying Vascular Lesions

Lesions with UCA flow identified using 4D View (GE - Kretztechnik, Zipf, Austria)

Axial imaging planes

3D rendered image

(trans up 3x the normal rate)
3D Volume Processing

An ROI corresponding to contrast flow is mapped on to the raw 3D slice data
Background Filtering

First 3 seconds of image data were used to develop a volumetric background template and filtered from the entire volume.
Analyzing Vascular Heterogeneity within the Lesion

P₁: Peripheral
C: Central
P₂: Peripheral
A total of 236 patients were enrolled in the study.

Image data was available for 219 patients.

17 cases were not included in the final analysis:
- 8 cases were excluded due to inability to access a peripheral vein.
- 9 cases were incomplete due to malfunction with the ultrasound scanner.
Pathology Results

Total number of benign lesions = 164
- 31.10% Fibroadenoma
- 13.41% Hyperplasia
- 1.22% Mastitis
- 18.90% Cysts
- 1.22% Fibroepithelial lesion
- 1.83% Intraductal Papilloma
- 4.88% Adenosis
- 8.54% Lymph node
- 2.44% Fat
- 16.46% Other

Total number of malignant lesions = 55
- 77.78% Invasive ductal carcinoma
- 12.96% Ductal carcinoma in situ
- 7.41% Invasive lobular carcinoma
- 1.85% Invasive papillary carcinoma
Vascular Heterogeneity

Malignant: invasive ductal carcinoma

<table>
<thead>
<tr>
<th>Relative change from baseline (dB)</th>
<th>Mean</th>
<th>Stdev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral 1</td>
<td>1.20</td>
<td>1.36</td>
</tr>
<tr>
<td>Central</td>
<td>4.87</td>
<td>3.39</td>
</tr>
<tr>
<td>Peripheral 2</td>
<td>3.03</td>
<td>1.74</td>
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</table>
Vascular Heterogeneity

Benign: Fibroadenoma

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<tr>
<td>Peripheral 1</td>
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<td>2.36</td>
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<tr>
<td>Peripheral 2</td>
<td>1.87</td>
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</tbody>
</table>
Vascular Heterogeneity

Area under ROC = 0.72
Locally Advanced Breast Cancer

LABC has not metastasized to distant tissue

IIIA:
Tumor size > 5 cm
AND
Cancer in axillary lymph nodes

IIIB:
Tumor of any size
AND
Cancer in lymph nodes above the collarbone

Neoadjuvant Chemotherapy is the Standard of Care for LABC

- Reduces the size of breast cancers
  - more conservative surgical options
- Same overall survival as for adjuvant chemotherapy (70% in ACT vs. 69% in NCT)
- Same disease free survival as for adjuvant chemotherapy (55% ACT and 53% NCT)
- Gives an early assessment of tumor response to chemotherapy

[Wolmark et al., J Natl Cancer Inst Monogr, 2001]
Interstitial Fluid Pressure (IFP) is Higher in Tumors than in Normal Tissue

- Typical IFP values:
  - Mean IFP in normal tissues: -1 to 3 mmHg
  - Mean IFP cancers: 10 to 30 mmHg

- Current method
  - Wick-in-needle technique
  - Invasive

- IFP may allow monitoring of response to neoadjuvant chemotherapy in breast cancer

[Heldin et al., Nat Rev Cancer, 2004]
Subharmonic Aided Pressure Estimation (SHAPE)

![Graph showing subharmonic signal reduction over 0 to 186 mmHg (dB) with linear regression](image)

| Sonazoid™ | 13.3 ± 0.2 | 0.99 |
| ZFX | 12.2 ± 0.2 | 0.97 |
| Definity® | 11.0 ± 0.3 | 0.98 |
| Optison™ | 10.1 ± 0.2 | 0.97 |
| Levovist® | 9.6 ± 0.2 | 0.98 |

[Halldórsdóttir et al., Ultrason Imaging, 2011]

Hydrostatic pressure (mmHg)

Subharmonic signal reduction (dB)

f\text{transmit}: 4.4 MHz
f\text{receive}: 2.2 MHz
Human Clinical Trial of IFP Measurements

- 17 patients with breast cancer
- Scheduled for neoadjuvant chemotherapy
  - clinical outcomes as reference
- 3D SHI at 0%, 10%, 60% and 100% of chemotherapy delivered
- Modified Logiq 9 with 4DL10 probe
- Definity infusion (3 mL in 50 mL saline) (IND: 112,241)
Automatic Power Optimization

[Dave et al., Ultrasonics, 2013]
Data Analysis Procedure

Select ROIs
(Tumor and surrounding regions)

Use the same ROIs for baseline and SHAPE

Calculate the subharmonic UCA signal change using the base data in each ROI

Calculate the max. magnitude of subharmonic signal from each ROI

Calculate the ratio between results from the tumor and the surroundings

Correlate with neoadjuvant therapy response (tumor size change)
Data Analysis

Results were grouped by complete or partial treatment response (> 90% reduction in tumor volume assessed by imaging) and compared with student’s t-test using Matlab (R2015b; Mathworks, Natick, MA, USA)

Changes in tumor volume were also correlated with treatment response
Results

Out of the 17 patients enrolled:

- 8 subjects completed all 4 scans
- 3 subjects completed 3 scans
- 6 subjects were lost to follow up (after 2 scans or less)

Of the 11 subjects followed to completion there were 6 complete responders and 5 partial responders
Example Case

52 year old woman with 2.8 x 2.2 cm triple negative breast cancer
Morning prior to starting neoadjuvant chemotherapy
Example Case

52 year old woman with 2.5 x 2.2 cm triple negative breast cancer
10% through course of neoadjuvant chemotherapy
Example Case

52 year old woman with 1.0 x 1.0 cm triple negative breast cancer
100% through course of neoadjuvant chemotherapy
SHAPE and SHI at 10% of Treatment

Responders vs. Nonresponders:

- SHAPE: 3.23 ± 1.41 dB vs. -0.88 ± 1.46 dB; \( p = 0.001 \)
- SHI: 1.32 ± 0.73 dB vs. -0.82 ± 0.88 dB; \( p = 0.002 \)
Portal Hypertension

- Portal pressure measurements are clinically useful for managing a variety of hepatic diseases.
- Currently these pressures are estimated as the difference between the free and wedged hepatic vein pressures - the hepatic venous pressure gradient (HVPG).
- Portal hypertension is defined as HVPG > 10 mmHg, while patients with HVPG > 12 mmHg are at risk for variceal rupture and increased mortality.

Noninvasive SHAPE measurements may be a useful alternative to catheter-based measurements of HPVG.
Clinical Study of SHAPE for Diagnosing Portal Hypertension

- 300 patients scheduled for a transjugular liver biopsy at TJU or HUP
  - HVPG measurements as reference
- Modified Logiq 9 scanner with 4C probe (Tx/Rx: 2.5/1.25 MHz)
- Output power optimized individually
- Gaussian windowed binomial filtered square wave
- Sonazoid 1.44 μL microbubbles/kg/hour (IND: 124,465)
Subharmonic Signal versus HVPG

![Graph showing the correlation between subharmonic signal and HVPG. The graph includes data points for clinical trials and pilot studies, with linear regression lines for each.](image-url)
Conclusions

SHI appear able to detect variations in vascular heterogeneity between central and peripheral regions for benign and malignant breast lesions ($p < 0.01$ & $A_z = 0.72$)

SHAPE has the potential to predict neoadjuvant chemotherapy response of breast cancer as early as at 10% completion of the therapy ($p < 0.002$)

Results in patients indicate SHAPE estimates of portal hypertension agree well with HVPG measurements ($N = 52$; $r = 0.79$)
THANK YOU!

“OK, folks! ... It's a wrap!”