Elasticity Imaging reaching Clinical Maturity

Andy Milkowski
Director Research and Development
Siemens Ultrasound

Objectives

Elasticity and Breast
ARFI / Shear Wave and Liver
Both are mature and adding to clinical practice

Imaging Mode Characteristics

B-Mode
- Echotexture
- Echogenicity
- Shape
- Size
- Shadowing
- Posterior enhancement

Doppler
- Resistive Index (RI)
- Turbulence
- Velocity
- Pulsatility

Strain
- Relative stiffness
- Shear wave speed
- Shape
- Size
“Bulls-Eye” appearance of cyst

Fibroadenoma and cyst

Biopsy Proven Benign Fibroadenoma

EI/B Ratio < 1.0
Biopsy Proven Breast Cancer

**EI/B Ratio >1.0**

### Table: Multi-Center Trial Results*

<table>
<thead>
<tr>
<th>Site</th>
<th>Total Lesion</th>
<th>Malignant Lesion</th>
<th>EI/B-mode Ratio ≥ 1</th>
<th>Sensitivity Malignant</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>251</td>
<td>54</td>
<td>54</td>
<td>100%</td>
<td>197 188</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>40</td>
<td>30</td>
<td>100%</td>
<td>39 26</td>
</tr>
<tr>
<td>3</td>
<td>208</td>
<td>95</td>
<td>87</td>
<td>95%</td>
<td>119 100</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>14</td>
<td>14</td>
<td>100%</td>
<td>38 29</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>18</td>
<td>18</td>
<td>100%</td>
<td>16 12</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>6</td>
<td>6</td>
<td>100%</td>
<td>7 6</td>
</tr>
<tr>
<td>Total</td>
<td>635</td>
<td>222</td>
<td>219</td>
<td>98.6%</td>
<td>413 361</td>
</tr>
</tbody>
</table>

Conclusion: Sensitivity and Specificity is reproducible across multiple centers

Richard G. Barr MD, PhD [1,2], Logan B. Lackey II MBA, BS [2], William E. Svensson MD [3], Corinne Balleyguier MD [4], Carmel Smith [5], Stamatia Destounis MD [6]

*Submitted for publication*
Current Status and Future

- Current Status
  - Traditional 2D/B-Mode imperfect
  - Litigation
  - Reimbursement model

- Future
  - CAD
  - Shape
  - Margins
  - Orientation
  - Echo pattern
  - Elasticity + B-mode
  - Payor system changes

Imaging Mode Characteristics

- B-mode
  - Echotexture
  - Echogenicity
  - Shape
  - Size
  - Shadowing
  - Posterior enhancement

- Doppler
  - Resistive index (RI)
  - Turbulence
  - Velocity
  - Pulsatility

- Speckle
  - Relative stiffness
  - Shear wave speed
  - Shape
  - Size

ARFI / Shear Wave Technology

ARFI / Shear Wave Velocity Estimation

* This product is not commercially available in the United States.
### Physics Extra – Motivation

<table>
<thead>
<tr>
<th>Example</th>
<th>Shear wave speed (m/s)</th>
<th>Bulk modulus (kPa)</th>
<th>Shear modulus (kPa)</th>
<th>Dilatational wave speed (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>1490 – 1540</td>
<td>2 – 2.5</td>
<td>0 – 0.3</td>
<td>0 – 0.5</td>
</tr>
<tr>
<td>Healthy liver</td>
<td>1490 – 1540</td>
<td>2 – 2.5</td>
<td>0.3 – 8</td>
<td>0.5 – 2.8</td>
</tr>
<tr>
<td>Muscle</td>
<td>1490 – 1540</td>
<td>2 – 2.5</td>
<td>1 – 10</td>
<td>1 – 3.2</td>
</tr>
<tr>
<td>Prostate</td>
<td>1490 – 1540</td>
<td>2 – 2.5</td>
<td>2 – 15</td>
<td>1.4 – 3.9</td>
</tr>
<tr>
<td>Myocardium</td>
<td>1490 – 1540</td>
<td>2 – 2.5</td>
<td>3.7 – 50</td>
<td>2.6 – 7.1</td>
</tr>
<tr>
<td>Fibrotic liver</td>
<td>1490 – 1540</td>
<td>2 – 2.5</td>
<td>10 – 100</td>
<td>3.2 – 10</td>
</tr>
</tbody>
</table>

### Fibrosis in Chronic Liver Disease

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Stage</th>
<th>Category description</th>
<th>Measurement*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fibrosis</td>
<td>F0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Fibrous expansion of small portal vein or short fibrous septa</td>
<td>F1</td>
<td></td>
<td>3 – 5%</td>
</tr>
<tr>
<td>Fibrous expansion of small portal veins with occasional short fibrous septa</td>
<td>F2</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Fibrous expansion of medium portal veins with occasional short fibrous septa</td>
<td>F3</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Fibrous expansion of portal veins with marked bridging (portal to portal)</td>
<td>F4</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>Portal bridging (P–P) and/or bridging (P–S) with marked dilatational wave</td>
<td>Minimal</td>
<td></td>
<td>15%</td>
</tr>
<tr>
<td>Cirrhosis, portal veins or definite</td>
<td>F0</td>
<td></td>
<td>F0</td>
</tr>
</tbody>
</table>

*Proportion (%) of area of illustration showing Shear wave speed for collagen (NADH-sensitive area, CP4)

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**Liver Fibrosis Staging**

- **F0**: Normal liver
- **F1**: Minimal fibrosis
- **F2**: Mild fibrosis
- **F3**: Moderate fibrosis
- **F4**: Advanced fibrosis

**Liver Fibrosis Staging**

- **Minimal/Mild Fibrosis**
  - $V_s = 1.14$ m/s
  - Negative
- **Moderate Fibrosis**
  - $V_s = 1.4$ m/s
  - Positive
- **Advanced Fibrosis**
  - $V_s = 3.51$ m/s
  - Positive
Conclusion: ARFI imaging and serum fibrosis marker test results correlated significantly with histologic fibrosis stage.

ARFI imaging is a promising US-based method for assessing liver fibrosis in chronic viral hepatitis.

Conclusion: There is a significant positive correlation between median velocity measured by using ARFI sonoelastography and severity of liver fibrosis in patients with NAFLD. The results of ARFI sonoelastography were similar to those of transient sonoelastography.

### ROC curves for ARFI imaging, TE, FibroTest, and APRI-based diagnoses of (a) moderate fibrosis (stage F2) and (b) cirrhosis (stage F4).

### Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Total N</th>
<th>AUROC 1</th>
<th>AUROC 2</th>
<th>AUROC 3</th>
<th>AUROC 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iijima et al (Japan)</td>
<td>CLD</td>
<td>160</td>
<td>0.887</td>
<td>0.869</td>
<td>0.897</td>
<td>0.903</td>
</tr>
<tr>
<td>Salat et al (Austria)</td>
<td>CLD (CSPH in 52%)</td>
<td>48</td>
<td>0.907</td>
<td>0.903</td>
<td>0.903</td>
<td>0.903</td>
</tr>
<tr>
<td>Sporea et al (Romania)</td>
<td>HCV, HBV (N=54.17)</td>
<td>183</td>
<td>0.902</td>
<td>0.893</td>
<td>0.903</td>
<td>0.903</td>
</tr>
<tr>
<td>Lupor et al (Romania)</td>
<td>HCV</td>
<td>74</td>
<td>0.901</td>
<td>0.905</td>
<td>0.911</td>
<td>0.911</td>
</tr>
<tr>
<td>Goertler et al (Germany)</td>
<td>HCV, HBV (N=36.21)</td>
<td>77</td>
<td>0.901</td>
<td>0.901</td>
<td>0.901</td>
<td>0.901</td>
</tr>
<tr>
<td>Friedrich-Rust et al (Germany)</td>
<td>HCV, HBV</td>
<td>81</td>
<td>0.904</td>
<td>0.904</td>
<td>0.904</td>
<td>0.904</td>
</tr>
<tr>
<td>Takahara et al (Japan)</td>
<td>CLD</td>
<td>80</td>
<td>0.904</td>
<td>0.904</td>
<td>0.904</td>
<td>0.904</td>
</tr>
<tr>
<td>Calabrese et al (Italy)</td>
<td>CLD</td>
<td>60</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Yoneda et al (Japan)</td>
<td>NAFLD</td>
<td>64</td>
<td>0.973</td>
<td>0.978</td>
<td>0.978</td>
<td>0.978</td>
</tr>
<tr>
<td>Barcelona Study</td>
<td>CLD, Transplants (N=46, 62)</td>
<td>111</td>
<td>0.805</td>
<td>0.805</td>
<td>0.805</td>
<td>0.805</td>
</tr>
<tr>
<td>Palmeri et al (Duke)</td>
<td>NAFLD</td>
<td>135</td>
<td>0.875</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Mean Values

<table>
<thead>
<tr>
<th>AUROC 1</th>
<th>AUROC 2</th>
<th>AUROC 3</th>
<th>AUROC 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.799</td>
<td>0.875</td>
<td>0.932</td>
<td>0.932</td>
</tr>
</tbody>
</table>
**Liver Fibrosis Clinical Utility Algorithm**

- **HCV genotype 1, 4, 5, or 6**
- **Approx 30% of Patients**
  - Positive (Predicted F≥3) → Treatment
  - Negative (Predicted F<3) → Repeat ARFI in 3-5 yrs

- **Approx 70% of Patients**
  - Positive (Predicted F≥3) → Treatment
  - Negative (Predicted F<3) → Clinical Monitoring

**ARFI / Shear Wave Clinical Applications**

Evaluation of Acoustic Radiation Force Impulse (ARFI) imaging and contrast-enhanced ultrasound in renal tumors of unknown etiology in comparison to histological findings


Conclusion: ARFI imaging improves visualization of unclear renal masses in comparison to fundamental B-scan and adds new information about the tissue stiffness in a less time-consuming and more reproducible way.

**Clinical Trend**

Recommendations (excerpt)

4) Assessment of the severity of liver fibrosis is important in decision making in patients with chronic hepatitis C.

5) Liver biopsy is still regarded as the reference method to assess the stage of fibrosis.

6) Transient elastography (TE) can be used to assess liver fibrosis in patients with chronic hepatitis C.
FDA and Regulatory Approval

- FDA Non-Substantial Equivalence Determination for Virtual Touch – Requires Pre-Market Approval (PMA) and Specific IFU

- Major concern of FDA in use of non-invasive diagnostic tests for liver fibrosis is clinical outcome risk of false negative or false positive results

- Diagnostic Accuracy must be proven with a science based, randomized, prospective clinical trial

- IFU: To demonstrate by receiver operating characteristics (ROC) analysis that quantitative ARFI can accurately diagnose advanced liver fibrosis (Ishak stages 3-6 / Metavir stages F3 or F4) non-invasively

Objectives

- Elasticity and Breast
  - ARFI / Shear Wave and Liver
  - Both are mature and adding to clinical practice