NONINVASIVE IMAGING METHODS FOR ASSESSMENT OF LIVER DAMAGE IN NASH

Bachir Taouli, MD
Director of Body MRI and Cancer Imaging Program
Department of Radiology / Translational and Molecular Imaging Institute
Icahn School of Medicine at Mount Sinai, NY
Goals of imaging in chronic liver disease/NAFLD

- Diagnose cirrhosis, portal hypertension and HCC
- Diagnose and quantify fat and iron
- Ultimate goals:
  - Diagnose inflammation and fibrosis
  - Reduce biopsy-related risks and costs
  - Facilitate earlier diagnosis
  - Improve monitoring of disease progression
  - Use in drug trials
  - Screening?
Liver cirrhosis
Morphologic changes for diagnosing cirrhosis (n=143)

<table>
<thead>
<tr>
<th>Measure</th>
<th>AUC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphologic changes</td>
<td>0.70-0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MELD score</td>
<td>0.63</td>
<td>0.094</td>
</tr>
<tr>
<td>APRI</td>
<td>0.69</td>
<td>0.565</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spleen volume (cm$^3$)</td>
<td>0.63</td>
<td>0.083</td>
</tr>
<tr>
<td>Hepatic arterial enhancement</td>
<td>0.67</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Kihira. Abd Radiology 2016
Elastography

- Induce shear waves in tissue
- Estimate velocity of shear waves
- Calculate stiffness from the velocity

\[ \mu = v^2 \rho \]

- Shear Stiffness
- Wave Velocity
- Tissue Density
FibroScan in NAFLD

<table>
<thead>
<tr>
<th>Stage</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥F2</td>
<td>0.84 (0.79-0.90)</td>
</tr>
<tr>
<td>≥F3</td>
<td>0.93 (0.89-0.96)</td>
</tr>
<tr>
<td>F4</td>
<td>0.95 (0.91-0.99)</td>
</tr>
</tbody>
</table>


Meta-analysis

**Significant fibrosis**

AUROC: 0.84 (0.82-0.86)

**Cirrhosis**

AUROC: 0.94 (0.93-0.95)

Friedrich-Rust et al. Gastroenterology 2008; 134: 960-74
Liver MRE

- Fibrosis induces changes in liver stiffness
- Stiffness: indirect marker of fibrosis
- Three step process:
  1. Generate mechanical waves within liver
  2. Image the micron-level displacements caused by propagating waves using oscillating motion-sensitizing gradients
  3. Process the wave images using an “inversion” algorithm to generate quantitative maps of mechanical properties

Muthupillai et al., Science 1995
Acoustic driver system for MRE

Acoustic waves at 60Hz

Elastogram

Courtesy, Richard Ehman; Mayo Clinic and Temel Yasar, ISMMS
Normal (Liver donor)           Cirrhosis

Wave images

Stiffness maps
### AUC of MRE

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Freq. (Hz)</th>
<th>Measurement</th>
<th>F≥1</th>
<th>F≥2</th>
<th>F≥3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yin 2007</td>
<td>85</td>
<td>60</td>
<td>Shear stiffness</td>
<td>-</td>
<td>0.921</td>
<td>0.920</td>
<td>0.919</td>
</tr>
<tr>
<td>Huwart 2008</td>
<td>127</td>
<td>65</td>
<td>Shear elasticity (storage modulus)</td>
<td>0.962</td>
<td>0.994</td>
<td>0.985</td>
<td>0.998</td>
</tr>
<tr>
<td>Asbach 2010</td>
<td>70</td>
<td>25-62.5</td>
<td>Shear modulus</td>
<td>0.913</td>
<td>0.924</td>
<td>0.974</td>
<td>0.993</td>
</tr>
<tr>
<td>Wang 2011</td>
<td>76</td>
<td>60</td>
<td>Shear stiffness</td>
<td>0.92</td>
<td>0.98</td>
<td>0.99</td>
<td>0.95</td>
</tr>
</tbody>
</table>
Performance of MRE for detection of liver fibrosis

- **Yin 2007**

- **Huwart 2008**

- **Asbach 2010**

- **Motosugi 2010**

- **Wang 2011**

- **Dyvorne Liver Int 2016**
MRE in NAFLD

- Recent study pooling data on NAFLD data from 9 centers (n=232)
- High diagnostic accuracy for fibrosis detection
- AUROCs of 0.87 (significant) and 0.90 for advanced fibrosis
- No effect of BMI on MRE performance

Singh et al, Eur Rad 2015
52 y old female with NASH
Normal liver morphology
LS-MRE 5.4 kPa, LS-ARFI: 2.7 kPa
Bx: Stage 3 grade 3

Wave image
Stiffness color map, scale 0-8 kPa

Taouli, Serfaty. Gastroenterology 2016
Fat percentage (%)  
R2 water

<table>
<thead>
<tr>
<th>T2 Corrected</th>
<th>Water Sig.</th>
<th>Lipid Sig.</th>
<th>Lipid Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE = 12</td>
<td>1.12e+08</td>
<td>1.73e+07</td>
<td>13.38</td>
</tr>
<tr>
<td>TE = 24</td>
<td>8.45e+07</td>
<td>1.33e+07</td>
<td>13.61</td>
</tr>
<tr>
<td>TE = 36</td>
<td>5.52e+07</td>
<td>1.09e+07</td>
<td>16.46</td>
</tr>
<tr>
<td>TE = 48</td>
<td>3.87e+07</td>
<td>8.18e+06</td>
<td>17.43</td>
</tr>
<tr>
<td>TE = 72</td>
<td>2.68e+07</td>
<td>6.38e+06</td>
<td>18.15</td>
</tr>
<tr>
<td>R2 (s-1)</td>
<td>1.53e+07</td>
<td>3.97e+06</td>
<td>20.61</td>
</tr>
<tr>
<td>R-square fit</td>
<td>20.07</td>
<td>20.49</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Performance of MRE compared to TE and serum markers

_Huwart et al, Gastroenterology 2008 (n=141)_

- MRE: higher success rate than TE and better diagnostic accuracy than TE and APRI for staging liver fibrosis
- AUC MRE (0.994 for ≥ F2, 0.985 for ≥ F3, 0.998 for F4) larger than those of TE, APRI, and TE/APRI combined (0.837, 0.709, and 0.849 for ≥ F2, 0.906, 0.816, and 0.936 for ≥ F3; 0.930, 0.820, and 0.944 for F4)
Imajo et al, Gastro 2016

- Comparison of MRI/MRE to TE for grading steatosis and fibrosis (n=142 with NAFLD).
- Higher AUROC using MRE vs. TE for predicting F2-F4 fibrosis (0.91 vs. 0.82, p=0.001) and cirrhosis (0.97 vs. 0.92, p=0.049).
- Performance of MRI > TE-CAP for detecting all grades of steatosis.
- Serum markers did not provide additional information over imaging.
- TE failed in 15 patients (10% of the study cohort), while MRE measurements were successful in all included subjects.
Our experience (all etiologies of liver disease)

Dyvorne et al, Liver Int 2016
Advantages and limitations of US elastography and MRI/MRE for detection of liver fibrosis and fat

<table>
<thead>
<tr>
<th>Benefits</th>
<th>US Elastography</th>
<th>MRI/MRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap</td>
<td>Cheap</td>
<td>Large sampling (better than US elastography)</td>
</tr>
<tr>
<td>Widely available</td>
<td>Widely available</td>
<td>High accuracy for fat quantification</td>
</tr>
<tr>
<td>Can be combined with HCC screening (except for Fibroscan)</td>
<td>Can be combined with HCC diagnosis</td>
<td>Can be combined with HCC diagnosis</td>
</tr>
<tr>
<td>Limitations</td>
<td>Limited accuracy for fat quantification</td>
<td>Not easily available, expensive</td>
</tr>
<tr>
<td>Failure (obesity, steatosis, ascites)</td>
<td>Failure (iron) for GRE sequence; contra-indications in some patients</td>
<td>Parameters not fixed (some variability across series)</td>
</tr>
<tr>
<td>Limited sampling (better than Bx)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Future directions

- Technical improvements: improve wave delivery, 2D EPI and 3D EPI sequence
- Mechanical properties other than stiffness
- Longitudinal monitoring of fibrosis / Response to therapy
- Compare with US: diagnostic accuracy, failure, cost effectiveness
- Assess confounding factors
Summary

- MRE: excellent method for staging fibrosis
- Slightly better than US elastography
- Need more data for separation of inflammation from fibrosis
- Potential role of LS-MRE as a biomarker of liver damage in NASH