Liver Fibrosis and Cirrhosis

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Disclosure

- Research grant: Bayer
Chronic liver disease

- Viral hepatitis:
  - HBV highly prevalent in Asia
  - HCV prevalent in US/Europe, soon eradicated with DAA
- NASH: will likely become the most prevalent cause of liver disease
- Other: Alcohol, AI, PSC, metabolic, etc...

Risks: fibrosis, cirrhosis, portal hypertension, end-stage liver disease, HCC
Role of liver biopsy

- Considered the reference standard by most hepatologists at initial diagnosis
- Roles:
  - Assess degree of fibrosis and necroinflammation
  - Determines prognosis
- Risks, poor patient acceptance, interpretation and sampling errors, difficult to repeat (Cadranel Hepatology 2000; Regev Am J Gastroenterol 2002; Bedossa Hepatology 2003)
- Liver biopsy cannot be used in population-based studies of NASH
METAVIR scoring system for fibrosis

Modified from Poynard
Morphologic Changes of Cirrhosis

- Irregular liver contour
- Nodular/reticular pattern of liver parenchyma
- Hypertrophy of left lobe and/or caudate lobe
- Atrophy of right lobe/sigt. 4
- Expanded gallbladder fossa sign
- Conventional CT/MRI not sensitive for detection of early cirrhosis and for diagnosis of fibrosis

Mitchell DG, et al. JMRI 1993
Ito K, et al. Radiology 1999
Ito K et al. JMRI 2003
# Morphologic changes for diagnosing cirrhosis (n=143)

<table>
<thead>
<tr>
<th>Measure</th>
<th>AUC</th>
<th>p</th>
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<tbody>
<tr>
<td>Morphologic changes</td>
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<tr>
<td>Child-Pugh score</td>
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<td>&lt;0.001</td>
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<tr>
<td>MELD score</td>
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<td>0.094</td>
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<tr>
<td>APRI</td>
<td>0.69</td>
<td>0.565</td>
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<td>Platelet count</td>
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<td>&lt;0.001</td>
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<tr>
<td>Spleen volume</td>
<td>0.63</td>
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<tr>
<td>Hepatic arterial enhancement</td>
<td>0.67</td>
<td>&lt;0.05</td>
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</table>

*Kihira. Abd Radiology 2016*
Elastography

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

\[ m = v^2 \rho \]

Shear Stiffness

Tissue Density

Wave Velocity
4 primary elastography techniques: TE, MRE, point shear wave elastography (pSWE), SWE

TE and pSWE: fixed sampling area size (fixed for TE)
2D-SWE: variable sampling
MRE offers (near) full organ coverage

Kennedy et al. Radiology 2018
## Quantitative elastography methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Availability</th>
<th>Cost</th>
<th>Evidence</th>
<th>Liver sampling area</th>
<th>ROI placement</th>
<th>Reported parameter (Unit)</th>
<th>Main reasons for failure/unreliable results</th>
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</thead>
<tbody>
<tr>
<td>TE</td>
<td>Widespread</td>
<td>Low</td>
<td>Excellent validation</td>
<td>Small</td>
<td>Restricted - no guidance</td>
<td>Young’s Modulus (kPa)</td>
<td>High BMI (M probe), ascites</td>
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<tr>
<td>ARFI</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate-good validation</td>
<td>Small (pSWE)</td>
<td>Medium (2D-SWE)</td>
<td>Flexible with US guidance</td>
<td>Young’s modulus (kPa) or wave speed (m/s)</td>
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<tr>
<td>MRE</td>
<td>Limited</td>
<td>High</td>
<td>Limited validation</td>
<td>Large</td>
<td>Large organ coverage</td>
<td>Complex shear modulus (kPa)</td>
<td>Liver iron deposition, large ascites, BMI, 3T (2D GRE)</td>
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</tbody>
</table>

*Kennedy et al. Radiology 2018*
Transient elastography (FibroScan®)

Courtesy, Laurent Castera, Hopital Beaujon, Clichy
Fibroscan examples
### Diagnostic performance of TE

<table>
<thead>
<tr>
<th>Author</th>
<th>Region</th>
<th>Probe</th>
<th>Etiology</th>
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<th>F2-F4</th>
<th>F3-F4</th>
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ARFI (pSWE) US

MRE
Liver 7.0 kPa
Spleen 14.1 kPa

ARFI
Liver: 5.1 kPa
Spleen: 14.4 kPa
Limitations of US elastography methods

- TE failure assessed in a study of 13,369 examinations using the M probe (Castera et al. Hepatology 2010)
  - TE failed in 3.1% of cases, unreliable measurements were acquired in a further 15.8% of cases.
  - BMI identified as a significant contributory factor
  - Introduction of XL probe has improved the reliability of TE in patients with NAFLD.
  - Reliable measurements were obtained in 73% of patients with the XL probe compared to only 50% for the M probe (Myers. Hepatology 2012)
- TE not suited for spleen measurements
- Confounding factors: ALT flares, cholestasis, congestive heart failure, excessive alcohol intake and acute viral hepatitis
- Influence of steatosis: conflicting data
- pSWE and 2D-SWE:
  - Failure rate low for both methods (5% for 2D-SWE, and 1% for pSWE)
  - Interplatform variability may be an issue
Acoustic driver system for MRE

Acoustic waves at 60Hz

Elastogram

Courtesy, Richard Ehman; Mayo Clinic and Temel Yasar, ISMMS
MRE: Image processing pipeline

- Magnitude image
- Phase image
- Colorized wave image
- Greyscale elastogram
- Colorized elastogram
- Confidence map
MRE examples
# Performance of MRE

<table>
<thead>
<tr>
<th>Author</th>
<th>Region</th>
<th>Sequence</th>
<th>Etiology</th>
<th>N</th>
<th>Success (%)</th>
<th>AUC</th>
<th>F2-F4 Cut-off (kPa)</th>
<th>AUC</th>
<th>F3-F4 Cut-off (kPa)</th>
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<th>F4 Cut-off (kPa)</th>
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<td>6.7</td>
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</tbody>
</table>
Performance of MRE for detection of liver fibrosis

Yin 2007

Huwart 2008

Asbach 2010

Motosugi 2010

Wang 2011
56 y HIV/HCV male
Normal liver morphology, high LS
Stage 4 on Bx
Limitations of MRE

- Failure in patients with iron deposition using 2D GRE-MRE
- Confounded by inflammation, cholestatis
- Expensive
- Not easily available

61 yo male, HCV and iron deposition
T2* = 6 ms

Failed GRE-MRE  EPI-MRE  T2* map
Future directions

- Technical improvements: improve wave delivery, 2D EPI and 3D EPI sequence
- Viscoelastic properties other than shear stiffness
- Longitudinal monitoring of fibrosis / response to therapy
- Role in PH
- Risk of HCC
- HCC response
HCC response

Viable HCC

Stiffness 11.6 kPa in HCC and 4.0 kPa in liver

Necrotic HCC

Stiffness: 2.6 kPa in HCC and 7.4 kPa in liver
EPI-MRE is better than GRE-MRE

3D MRE acquisition

Non cirrhotic

Mean stiffness

Storage modulus

Cirrhotic

Loss modulus
MRE in portal hypertension

Liver 7.0 kPa
Spleen 14.1 kPa
Summary

- ARFI methods have shown similar diagnostic ability to TE with slightly higher reliability
- MRE: equivalent to slightly better diagnostic accuracy than TE and ARFI methods, while providing stiffness measurement over a larger area of the liver; however the method requires wider validation, and the higher cost and limited availability may limit adoption worldwide.
- In liver referral centers performing a large number of MRI exams, it is feasible to incorporate MRE into the standard imaging protocols to provide a fibrosis staging tool.
- New directions:
  - Faster and more reliable MRE sequences
  - Spleen MRE in portal hypertension

R1 maps (R1) maps. R1 maps acquired (A) pre and (B) one hour post EP-3533 in a rat fibrosis model.
Taouli Lab (Translational and Molecular Imaging Institute/ISMMS)

Octavia Bane, PhD; Sara Lewis, MD; Stefanie Hectors, PhD; Paul Kennedy, PhD; Daniela Said, MD; Naik Vietti Violi, MD; Daniel Stocker MD; Miriam Hulkower MD; Amy Law MD; Jeff Gnerre MD, Maxwell Segall, BS; Jonathan Rosenblatt, BA; Yair Bitton MBA

Funding:
- NIDDK Grant 1F32DK109591
- NCI Grant U01 CA172320
Elastography background

- To measure elasticity, stress is applied via shear wave propagation, delivered as a transient impulse or as a continuous dynamic excitation, and resulting tissue deformation is measured.
- Various methods of mechanical property quantification via transient and dynamic elastography have been developed using both US- and MR-based techniques.
- Elastography measures shear modulus (G, or the resistance to a shear stress) or Young’s modulus (E, often referred to as the elastic modulus), both in kPa.
- Under simplifying assumptions of incompressibility, E and G are approximately proportional: $E \approx 3G$.
- MRE: most reported parameter reported is the “shear stiffness”
Non invasive methods

**US elastography**

- Liver stiffness

**MRE**

- Liver stiffness

**Blood tests**

**DWI**

- ADC apparent diffusion
- D true diffusion
- PF perfusion fraction
- D* pseudo-diffusion

**DCE-MRI**

- Modeled parameters
  - Fa arterial flow
  - Fp portal venous flow
  - ART arterial fraction
  - DV distribution volume
  - MTT mean transit time

- Model free parameters
  - TTP time to peak
  - Cpeak peak [Gd]
  - AUC60 integral at 60s
## Diagnostic performance of pSWE and SWE

<table>
<thead>
<tr>
<th>Author</th>
<th>Region</th>
<th>Method</th>
<th>Etiology</th>
<th>N</th>
<th>Success (%)</th>
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<th>F3-F4</th>
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Cut-off values in kPa for 2D-SWE and m/s for pSWE
Mount Sinai experience with 2D GRE (Wagner. Radiology 2017)

- 781 MRE exams (in 691 patients) assessed for quality
- Technical failure rate of liver MRE higher at 3.0T compared to 1.5T using a 2D GRE sequence (failure rate: 15.3% vs. 3.5%)
- Univariate analysis, BMI, liver iron deposition, massive ascites, use of 3.0T, presence of cirrhosis, alcoholic liver disease were all significantly associated with failure
- Multivariable analysis, only BMI, liver iron deposition, massive ascites and use of 3.0T were significantly associated with MRE failure
Pitfall: All that’s stiff isn’t fibrosis

44yo M HCV with acute increase in LFT’s, abdominal pain

![Image of stiffness measurement]

Stiffness 10kPa

Biopsy: Mild-moderate fibrosis with moderate-severe necroinflammation

Courtesy of Scott Reeder, UW
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)
Comparison of MRI/MRE to TE for grading steatosis and fibrosis in NAFLD

- Imajo et al, Gastro 2016
- 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=
- Serum markers did not provide additional information over imaging markers
- TE failed in 15 patients (10% of the study cohort), while MRE measurements were successful in all included...
Tissue analysis

- Histologic methods
  - H&E, Trichrome, Sirius Red
  - Morphometry
- Immunostaining:
  - Alpha smooth muscle actin
  - Other HSC markers
- mRNA Quantification
  - Real time PCR with linear amplification from bx
Goals of imaging in chronic liver disease

- Diagnose cirrhosis, portal hypertension and HCC
- Quantify liver 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