EMERGING MRI TECHNIQUES FOR LIVER FIBROSIS

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• Nothing to disclose.

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Learning Objectives

• Discuss the clinical relevance of detection and characterization of liver fibrosis.

• Discuss MRI techniques that may play a role in noninvasive assessment of liver fibrosis.

• Discuss recent human studies of emerging MRI techniques for assessment of liver fibrosis.
Pediatric Chronic Liver Diseases & Fibrosis

• Many causes
  – Hepatitis (infection, autoimmune)
  – Biliary obstruction (BA, PSC, CF)
  – Iron, copper deposition
  – Steatosis/ NASH
  – Metabolic/ genetic defects (α-1 antitrypsin)

• Chronic injury (inflammation/necrosis) →
  myofibroblast activation → fibrogenesis (scarring)
Liver Fibrosis Staging by Biopsy

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Ishak stage: Categorical description</th>
<th>ISHAK</th>
<th>METAVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fibrosis (Normal)</td>
<td>Fibrosis expansion of some portal areas with short fibrous septa</td>
<td>1</td>
<td>F1</td>
</tr>
<tr>
<td>Fibrosis expansion of most portal areas with occasional portal to portal (P-P) bridging</td>
<td>2</td>
<td>F2</td>
<td></td>
</tr>
<tr>
<td>Fibrosis expansion of portal areas with marked portal to portal (P-P) bridging as well as portal to central (P-C)</td>
<td>3</td>
<td>F3</td>
<td></td>
</tr>
<tr>
<td>Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)</td>
<td>4</td>
<td>F4</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis, probable or definite</td>
<td>5</td>
<td>F5</td>
<td></td>
</tr>
</tbody>
</table>

- **METAVIR**
  - F0 (no fibrosis) – F4 (cirrhosis)

- **Ishak Grading**
  - Stage 0 (no fibrosis) – Stage 6 (Cirrhosis)

- New scoring system: NAS, SAF, NASH CRN – accounts for ballooning and lobular inflammation.


Diagnosis of Liver Fibrosis

• Because of biopsy’s limitations, there is a critical unmet need for noninvasive markers of liver fibrosis that are needed for detecting, measuring and following liver fibrosis.

• Ideal noninvasive marker for fibrosis
  – Liver fibrosis specific
  – Independent of underlying metabolic liver alterations
  – Simple/fast/reproducible across scanners/vendor platforms
  – Able to discriminate between different fibrosis stages
  – Able to predict clinical outcomes
Liver Fibrosis staging – MRI

- MR Elastography, Mayo Clinic (Resoundant)
- T1/cT1 mapping, commercialized by Perspectum Diagnostics (UK)
- T2 mapping, Magnepath (Australia)
- Texture analysis, Resonance Health (aka. Ferriscan)
- Other methods: T1rho, DWI-IVIM, etc.
Liver MR Elastography (MRE)

Longer wavelength = stiffer tissue
MRE indirectly detects/measures liver fibrosis
MRE Concept

- MR images are acquired with GRE sequence as the waves are propagating through the liver.
- The velocity and wavelength depend on the stiffness of the tissue (i.e. the velocity and wavelength increase with greater tissue stiffness.)
- Thus, images of propagating waves can be used to estimate stiffness

Liver fibrosis staging by MRE

Mean liver stiffness increases with the increased fibrosis stage in patients. Shown is a summary of the mean shear stiffness measurements of the liver for the 35 normal volunteers and the 48 patients divided into the 5 different fibrosis stages, which are indicated as F0, F1 . . . F4.

Reference: Meng Y, Ehman RL et Al., 2007

Image Courtesy – Dr. R. Ehman
Liver fibrosis staging by MRE – Meta-analysis

- Data from 12 studies (2003 – 2013)
- 697 MRE exams with biopsy correlation
- Failure rate was 4.3%
- 3.45 kPa cut-off (F0-1 vs. F2-4)
  - 73% sensitivity
  - 79% specificity

- 2D GRE MRE is the most widely used and accepted method MRI based method for staging of liver fibrosis.
- It is FDA approved and is commercially available on 3 major vendor platforms and at both 1.5T and 3T.
- However it has limitations. MRE is indirect measure and is confounding to presence of inflammation, congestion, iron and presence of high fat.

Reference: Singh S., Ehman RL et Al., 2015
Relaxation Mechanisms

• T1 Relaxation (Longitudinal)
• T2 Relaxation (Transverse), T2\* Relaxation

T1 Relaxation:
RF off

\[
\frac{dM_z}{dt} = -\frac{(M_z - M_0)}{T_1}
\]

• exponential recovery (T1=100-3000 ms, longer for higher B_0)
Relaxation Mechanisms

- T2 Relaxation (Transverse)

\[ \frac{dM_{xy}}{dt} = -\frac{M_{xy}}{T_2} \]

- exponential decay (T2 \(\approx\) 50-1000 ms)
To measure tissue T1 relaxation:
(MOLLI – modified Look-Locker inversion recovery)
T1 mapping using MOLLI with 5(3)3 pattern
If liver iron was elevated, a correction factor was applied, in particular the MR fibrosis score was increased. As one example, with a $T2^* ): 13-15\text{ms}$, then the score was increased by $+1$; moderate iron overload ($T2^* ): 11-13\text{ms}$ added $+2$, severe iron loading ($T2^* ): 7-11 \text{ms}$ added $+3$, and toxic iron overloading ($T2^* <7\text{ms}$) added $+6$.

cT1 = T1 – 420 + (20 X T2* measured)
Liver fibrosis staging by cT1

T1 is confounded by presence of iron. 
cT1 = corrected T1; corrected for presence of iron 
cT1=T1 – 420 + (20 X T2* measured)

Reference:
Review: T2 relaxation mechanism

- T2 Relaxation (Transverse)

- exponential decay (T2 ≈ 50-1000 ms)
Liver fibrosis grading by T2 mapping

Example images: (A) TE: 60 msec; (B) TE: 120 msec

Absolute T2 measurements (control 65.4±2.9 ms; mild (Ishak 1–2) 66.7±1.9 ms; moderate (Ishak 3–4) 71.6±1.7 ms; severe (Ishak 5–6) 72.4±1.4 ms), which demonstrated low standard error (~2.9 ms).

Reference: Guimaraes et Al. T2 relaxation time is related to liver fibrosis severity. QIMS, 2016.
Liver fibrosis grading by T2 mapping

Image courtesy: Paul Clark, Ph.D.
CTO, Magnepath, Australia.
Theory of T1-rho for liver: T1-rho is sensitive to slow-precessing protons such as collagen and proteoglycan. Increase in liver fibrosis increases the proteoglycan content and hence is proportional to T1-rho values.

- $v_1=500 \text{ Hz} \sim \text{frequency of slow motional interactions}$
- i.e. chemical exchange, rotational correlation time
Fourteen subjects, seven healthy (age = 27–65 years old) and seven patients (age = 40–70 years old) with liver fibrosis underwent MRI on 1.5 T clinical scanners.

T1ρ maps of healthy human liver (a) and patients liver corresponding to fibrosis stage of 1, 2, 3 and 4 respectively.

References: Anup Singh, Reddy 2015
Bar graph of T1ρ values corresponding to different groups based upon fibrosis stage. Group-0 contains healthy subjects, group-1 contains stage-1 fibrosis, group-2 contains stage-2 fibrosis and group-3 contains stage-3 or 4 fibrosis. Fibrosis score are based upon METAVIR scale (0–4).

References: Anup Singh, Reddy 2015
Liver fibrosis by T1 rho

Ten healthy control subjects (n = 6 female, n = 4 male; mean age 42.7 ± 12.4 years; age range 27–65 years) and 21 patients (n = 5 female, n = 16 male; mean age 56.5 ± 12.1 years; age range 23–80 years) with clinically/laboratory diagnosed liver cirrhosis were recruited.

Segmented T1-rho map of a 28-year old healthy control subject (A) and a 45-year old patient with liver cirrhosis (B). T1-rho value of the healthy subject was 49.1 ms and T1-rho value of the patient with liver cirrhosis was 55.7 ms.

Reference: Rauscher 2014, EJR
Diffusion weighted imaging (DWI)

- **DWI signal decay measured at diffusion scales (b-values)**

- **Slow diffusion**: Brownian motion of water molecules
- **Fast diffusion**: Microcirculation of intravascular molecules in the micro-capillaries
Bi-exponential Intra-voxel Incoherent Motion (IVIM) Signal Decay Model (LeBihan, 88)

\[ f(\Theta, i) = S_0 \left( f \exp(-b_i(D + D^*)) + (1 - f)(\exp(-b_iD)) \right) \]

- \( f \) – Capillaries' volume
- \( D \) – Tissue cellularity
- \( D^* \) – Blood flow

Graph showing the relationship between log signal and b-value.
Liver fibrosis staging by IVIM

- $D^*$: diffusion in intra-vascular compartment; $D$: diffusion in extra-vascular compartment. $f/PF$: perfusion fraction.

- Meta: Analysis: Data from 6 studies (inception – 2015) with biopsy correlation.
- 406 DWI-IVIM MRI scans were included.
- Comparison/ ability to detect F0-1 with F2-3 and F1-2 with F3-4.
- Significant difference in $D^*$ and $f$; $D$ showed no differences.

Drawbacks:
- Image acquisition is very long; 15 – 20 mins.
- Post-processing method still evolving.

(Zhang et Al. 2016: Intra-voxel Incoherent Motion MR Imaging for Staging of Hepatic Fibrosis)

Taouli et Al. JMRI 2010
Image based Texture analysis
Feature Extraction

STEP BY STEP
Currently used by governments and private firms across the world, facial recognition is considered the least intrusive of biometric technologies.

- **CAPTURING**: The foremost requirement is to capture the image and that can be done by scanning existing images or using cameras.
- **EXTRACTING**: Unique facial data is then extracted from the sample.
- **COMPARING**: The data is then compared with the database.
- **MATCHING**: The software then decides whether the sample matches any picture in the database or not.

Some of the places such systems are either being used or could be used:
- Airports
- Railway stations
- Banks & financial institutions
- Stadiums
- Public transport
- Government offices
- Business establishments

Graphic: Yatish Rothana/Mint
Source: Mint research
Liver fibrosis staging by Texture Analysis

Maximum Image contrast is key for success.

Comparison between quantitative versus qualitative histology.

Reference: Claude Sirlin 2015 BioMed Research
Liver fibrosis staging by Texture Analysis

Multi-TE T2W sequence for Image acquisition

At CCHMC: Liver MRE & Liver T1 comparison

R1myo = 1/T1myo-post − 1/T1myo-pre;
R1blood = 1/T1blood-post − 1/T1blood-pre;
ECV = R1myo/R1blood × (100 − HCT);
where ECV and HCT are give as percentage.

Reference: JCMR; Bluemke et Al. Myocardial T1 and Extracellular Volume Fraction Mapping at 3 Tesla

Reduction rate of T1 values = \[\frac{T1_{pre} - T1_{post}}{T1_{pre}} \times 100\ (%)\]
16 year old male with auto-immune hepatitis undergoing treatment.
To summarize:

- Multiple emerging quantitative MRI methods for staging liver fibrosis.

- Which individual method is sensitive and works best for which patient population and for which disease conditions are yet to be determined.

- A multi-parametric approach may have the best diagnostic performance.
THANK YOU

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