MRI of Diffuse Liver Disease  
Tuesday May 8, 2012 11 am  
Claude B. Sirlin, MD  
Liver Imaging Group, Dept. of Radiology, UCSD  
csirlin@ucsd.edu

NOTE: Participants who wish to receive a pdf of this lecture may contact me at the email address above.

Overview  
This is lecture 3 of 4 in the Liver MRI Session of the Clinical Intensive Course. The first two lectures discussed liver specific contrast media and cancer in the difficult liver. This lecture discusses MRI of diffuse liver disease, as outlined briefly below and discussed in greater detail in the lecture itself.

Objectives  
The objectives of this lecture are to
- Review basic concepts about diffuse liver disease  
- Review basic concepts about biomarkers of diffuse liver disease
  - Histology-based biomarkers  
  - Imaging-based biomarkers
- Evaluate the use of MR-based biomarkers for assessment of the following histology-based biomarkers:
  - Steatosis
    - MR signal fat fraction  
    - MR proton density fraction
  - Iron overload
    - MR signal intensity ratios
    - R2  
    - R2*
  - Liver fibrosis
    - Diffusion-based biomarkers  
    - MRE-based biomarkers
Outline

I. Introduction

The introduction will briefly review the following basic concepts:

- Diffuse liver disease
  - Diffuse liver disease encompasses a broad spectrum of conditions with multiple etiologies, manifestations, co-morbidities, natural histories, outcomes, and management strategies.
  - Diagnosing, grading, and staging diffuse liver disease is important for prognostication, clinical decision making, monitoring response to therapy, research, and clinical trials.
  - The current “gold standard” for diagnosing, grading, and staging liver disease is tissue sampling (usually via core biopsy performed percutaneously) with histological evaluation.
  - Multiple histological features may be evaluated depending on the specific form of liver disease. These histological features are not the disease itself, they are biomarkers of the disease (see below).
  - A full discussion of the large number of available histology-based biomarkers is beyond the scope of this lecture. Important histology-based biomarkers include steatosis, iron overload, and fibrosis, and these are the histology-based biomarkers that will be emphasized in the lecture.
  - While they comprise the current gold standard for clinical care and clinical trials, histology-based biomarkers have important limitations for diagnosis, grading, and staging liver disease. The most important limitations are (a) their acquisition requires an invasive procedure (e.g., biopsy) and so they are not suitable for frequent testing or many types of research and (b) they are prone to sampling error.
  - Imaging-based biomarkers are being developed to address the need for non-invasive evaluation of diffuse liver disease.

- Biomarkers of diffuse liver disease
  - A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
  - Histological features of diffuse liver disease do not represent the disease itself. They are indicators of processes and responses associated with the disease and hence are themselves biomarkers.
  - An imaging biomarker is a characteristic that is objectively measured using an imaging technique and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
  - Many imaging-based biomarkers have been or are being developed using a broad spectrum of modalities including US, CT, MR, and PET. A full
discussion of all the potential imaging-based biomarkers is beyond the scope of this lecture.

- This lecture will focus on the following MR-based biomarkers:

<table>
<thead>
<tr>
<th>Histology-based biomarker</th>
<th>Corresponding MR-based biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>MR signal fat fraction (FF)</td>
</tr>
<tr>
<td></td>
<td>MR proton density fat fraction (PDFF)</td>
</tr>
<tr>
<td>Iron overload</td>
<td>MR signal intensity ratios</td>
</tr>
<tr>
<td></td>
<td>R2</td>
</tr>
<tr>
<td></td>
<td>R2*</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Diffusion-based biomarkers</td>
</tr>
<tr>
<td></td>
<td>Exponential model: ADC</td>
</tr>
<tr>
<td></td>
<td>Bi-exponential model: $D_{\text{fast}}$, $D_{\text{slow}}$, $D_{\text{fast fraction}}$</td>
</tr>
<tr>
<td></td>
<td>MRE-based biomarkers</td>
</tr>
<tr>
<td></td>
<td>Stiffness</td>
</tr>
<tr>
<td></td>
<td>Rheological model: elasticity, viscosity</td>
</tr>
</tbody>
</table>

- Evaluating the performance characteristics of imaging-based biomarkers of diffuse liver disease
  - Key performance characteristics include:
    - Accuracy against an independent and appropriate reference standard
    - Precision
      - Technical
        - Repeatability
        - Reproducibility
        - Robustness
      - Biological
        - Temporal variability
        - Spatial distribution

II. MR-Based Biomarkers of Steatosis
This section will address the following basic questions:
- What is steatosis?
- Why is it important?
- How is it diagnosed and graded using histology?
- What is the MR signal fat fraction?
- What are the critical confounders that corrupt the MR signal fat fraction as a biomarker of steatosis
- How can these confounders be minimized or corrected to estimate the MR proton density fat fraction?
What are the performance characteristics of MR proton density fat fraction for diagnosing and grading steatosis?

Future directions

II. MR-Based Biomarkers of Iron Overload
This section will address the following basic questions:
- What is iron overload?
- Why is it important?
- How is it diagnosed and graded using histology and using biochemical assay?
- What is the MR signal intensity ratio and how is it measured?
- What are the performance characteristics of MR signal intensity ratio for diagnosing and grading iron overload? What are the advantages and disadvantages of this method?
- What is R2 and how is it measured?
- What are the performance characteristics of R2 for diagnosing and grading iron overload? What are the advantages and disadvantages of this method?
- What is R2* and how is it measured?
- What are the performance characteristics of R2* for diagnosing and grading iron overload? What are the advantages and disadvantages of this method?

Future directions

III. MR-Based Biomarkers of Liver Fibrosis
This section will address the following basic questions:
- What is liver fibrosis?
- Why is it important?
- How is it diagnosed and staged using histology?
- What are diffusion-based biomarkers of liver fibrosis and how are they measured? What are the performance characteristics of diffusion-based biomarkers for diagnosing and staging liver fibrosis? What are the advantages and disadvantages of diffusion-based biomarkers?
- What are MRE-based biomarkers of liver fibrosis and how are they measured? What are the performance characteristics of MRE-based biomarkers for diagnosing and staging liver fibrosis? What are the advantages and disadvantages of MRE-based biomarkers?

Future directions

IV. Summary and Conclusions