NON INVASIVE EVALUATION OF DISEASE PROGRESSION IN CHRONIC LIVER DISEASES

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Early to Advanced Liver Fibrosis

Cirrhosis without Clinical Manifestations

Cirrhosis with Clinical Manifestations

Liver Failure

HVPG 5-10 mm Hg

HVPG 5-10 mm Hg

HVPG > 10-12 mm Hg

Spleen-related Noninvasive Indexes & Algorithms

Spleen Stiffness Measurement

Liver Stiffness Measurement

Serum Markers: Direct/Indirect

Serum Markers: predictors of liver related outcomes

Liver Biopsy (PC or TJ): Quantitative staging with CPA

Search for early predictor of decompensation and ACLF

Search for early predictor of HCC

Search for predictors of progression rate to cirrhosis

Advanced Chronic Liver Disease

HVPG < 5 mm Hg

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Non Invasive Evaluation of Liver Tissue Fibrosis (Staging)

- Liver Biopsy: 1:50,000 of liver tissue
- Serum Markers
- Imaging: US, TC, MRI
- Elastography (FibroScan, MRE, ARFI, Supersonic etc.)
- HVPG
  - Valuable only in cirrhosis

VERY IMPERFECT GOLD STANDARD FOR NON INVASIVE METHODS

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End-Points in Fibrogenic CLDs

F: METAVIR
S: ISHAK’s
K: KLEINER

Screening for Oesophageal Varices
Screening for HCC

Indication for Treatment

S0
S1&2
S3
S4-S5
S6
K/F0
K/F1
K/F2
K/F3
K/F4

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Liver Biopsy

1. Provides clues about etiology and co-factors
2. Allows immunohistochemical, biochemical biomolecular, genetic and epigenetic investigations
3. Allows assessment of iron/copper content
4. Is employed for grading (ACTIVITY) and staging (FIBROSIS), but .............

is a very imperfect GOLD STANDARD for non invasive methods
Liver Biopsy: Inter-Observer Diagnostic Accuracy

Observers: n. 3
Samples: n. 234

% Concordant/Discordant

Central Metavir Biopsy Score


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Established and Candidate Serum Biomarkers of Liver Fibrosis

- **“Indirect”: Not related to Fibrogenesis**
  - AST, ALT, gGT, Apolipoprotein A1, bilirubin, a2-macroglobulin, haptoglobin, cholesterol
  - HOMA-IR, HOGIS
  - Platelets, INR/PT

- **“Direct”: ECM components and enzymes**
  - HA, PIIINP, Collagen IV, Collagen VI, TIMP-1, Laminin, YKL-40, Tenascin, Undulin, MMP-1, MMP-2
Circulating Matrix Proteins Related to Fibrogenesis and Fibrolysis

Shedding products of both Fibrogenesis and Fibrolysis may derive from chronic diseases in other organs and systems (i.e. arthritis, atherosclerosis, pulmonary fibrosis etc.) and may be influenced by age and gender.
Misclassification Rate of Some Commonly Used Serum Markers

N= 1056 HCV patients
Cales P. et al. Liver Int 2009
Non Invasive Evaluation of Liver Tissue Fibrosis (Staging)

Liver Biopsy: 1:50,000 of liver tissue

Serum Markers

Imaging: US, TC, MRI

Elastography (FibroScan, MRE, ARFI, Supersonic etc.)

HVPG
1. The probe induces an elastic wave through the liver.
2. The velocity of the wave is evaluated in a region located from 2.5 to 6.5 cm below the skin surface.
3. The velocity of the wave is related to liver stiffness and to fibrosis.
4. Liver biopsy 1/50,000 of the liver; Fibroscan® 1/500 of the liver.
Fibroscan Limitations and Confounding Factors

1.- BMI > 30 and obesity
2.- Presence of ascites
3.- Flares of necroinflammation, hepatocyte swelling and steatosis (ETOH)
4.- Cholestasis
5.- High liver tissue iron content
6.- Fasting < 2 hours
### Fibroscan’s Challengers

**PROS & CONS**

<table>
<thead>
<tr>
<th><strong>ARFI</strong></th>
<th><strong>SWE</strong></th>
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<tbody>
<tr>
<td><strong>PROS</strong></td>
<td><strong>PROS</strong></td>
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<tr>
<td>Can be implemented on a regular US machine</td>
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<tr>
<td>High applicability</td>
<td>High range of value (2 – 150 kPa)</td>
</tr>
<tr>
<td>Performance equal to TE</td>
<td>Performance higher than TE</td>
</tr>
<tr>
<td><strong>CONS</strong></td>
<td><strong>CONS</strong></td>
</tr>
<tr>
<td>Results on meter/sec</td>
<td>Further validation needed</td>
</tr>
<tr>
<td>Narrow range of values</td>
<td>Quality criteria not defined</td>
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<tr>
<td>Quality criteria not defined</td>
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</tbody>
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Very high intra- and inter-observer variability

Need US skills and experience

_Berzigotti & Castera. J Hepatol 2013; 59: 180-2_
Fibroscan Applications in Liver Diseases

1.- Chronic Viral Hepatitis (cross-sectional)
2.- Chronic Viral Hepatitis (longitudinal and prognostic)
3.- Alcoholic Hepatitis
4.- NAFLD & NASH
5.- Cirrhosis and Portal Hypertension
6.- Liver Involvement in Systemic Diseases (Storage, Amyloidosis, Hemathology etc)
Hepatitis C: cut-offs

PPV: 88-95%  
NPV: 48-56%

PPV: 71-87%  
NPV: 81-93%

PPV: 77-78%  
NPV: 95-97%

Ziol et al. Hepatology 2005; 41: 48-54
TE for Fast Patient Allocation
Suspected Chronic HCV/HBV Hepatitis

FIBROSCAN

- **≤6 kPa**
  - No significant fibrosis
    - F0/S0
    - No biopsy
    - Possible implementation with other NIT

- **Intermediate values**
  - Gray area
    - Biopsy if results influence management

- **≥ (11)12 kPa**
  - Advanced fibrosis-cirrhosis
    - F1/S1
    - F2/S2
    - F3/S3-4
    - F4/S5-S6
    - No biopsy

Possible implementation with other NIT
Noninvasive Tests for Fibrosis and Liver Stiffness Predict 5-Year Outcomes of Patients with Chronic Hepatitis C

JULIEN VERGNIOL,* JULIETTE FOUCHER,*‡ ERIC TERREBONNE,* PIERRE-HENRI BERNARD,‡ BRIGITTE LE BAIL§,‖ WASSIL MERROUCHE,* PATRICE COUZIGOU,* and VICTOR DE LEDINGHEN*‖

Overall survival (%)

Follow-up (months)

≤9.5 kPa

>9.5 kPa

>30 kPa

>20 kPa

>40 kPa

>50 kPa

P < .0001
Non Invasive Measures Including Spleen Parameters

**Platelet count/spleen diameter ratio (Plt/Spl)**


**Liver stiffness x spleen diameter/platelet count (LSPS)**

The Spleen in the Assessment of Advanced Chronic Liver Disease

- Congestion
- Hypertrophy and Hyperplasia
- Fibrosis

Increase in spleen stiffness??

Encephalopathy

Ascites

Portal hypertension

Cirrhotic liver

Varices

Splenomegaly

Fibrosis

Hypertrophy and Hyperplasia

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Measurement of Spleen Stiffness by Fibroscan

1. – Sufficient intercostal space width
2. – Splenic parenchymal thickness > 4 cm (by US)
3. – Success rate > 60% and IQR < 30% of median value
4. – Intra-observer reproducibility 96%, inter-observer reproducibility 94%
5. – Probe upper limit 75 kPa
Spleen Stiffness (SS), a Promising Diagnostic Parameter in Cirrhosis
Colecchia A. et al., Gastroenterology 2012; 143(3):646-54

Esophageal Varices: NO
Esophageal Varices: YES

“Compensated” Cirrhosis

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Liver and Spleen Stiffness for the Prediction of the Presence of Esophageal Varices

Colecchia A. et al., Gastroenterology 2012; 143(3):646-54
Molecular Imaging of Collagen

DEC-MRI with EP-3533 contrast

Courtesy of Dr. Annalisa Berzigotti, Hospital Clinic Barcelona

Fuchs BC et al. J Hepatol 2013, in press
Measuring Collagen Content: What Are We Missing?

- Increasing tissue hypoxia and endothelial dysfunction
- Neoangiogenesis and microthrombosis
- Activation of the stem cell compartment
- Ductular reaction and "reactive" cholangiocytes
- Unbalanced vasoconstrictors and scar contraction
- Hepatocyte necrosis/apoptosis, inflammatory infiltration

All potential targets for bio-imaging and functional imaging

Measuring Collagen Content: What Are We Missing?
Possible molecular markers to be exploited:

Elastin, Collagen cross-linking: IRREVERSIBILITY

Immunophenotype, macrophage markers: REVERSIBILITY

BR55: A lipopeptide-based VEGFR2-targeted US contrast agent for molecular imaging of angiogenesis

Pochon et al. Invest Radiol 2010
Willmann et al Radiology 2008

Binding is amplified by ARF
