Updates on transient elastography

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Disclosures

- AbbVie
- Gilead
- BMS
- MSD
- Intercept Pharma
- Echosens
- Supersonic Imagine
- Mayoli
Liver stiffness evaluation

Quasi-static

Real-Time Elastography

Shear wave-based elastography

Mecanical push

Transient elastography FibroScan

Focused acoustic beams

ARFI

SuperSonic SW Imaging

Dynamic

Elasto-MR
Liver stiffness and Controlled Attenuation Parameter

- Stiffness
  - fibrosis
- CAP
  - steatosis

M probe
BMI 30 kg/m²
XL probe

CAP : 100 to 400 dB/m
E : 2 to 75 kPa
Many liver lesions are associated with liver stiffness

Liver stiffness

- Portal fibrosis
- Cholestasis
- Sinusoidal fibrosis
- Portal flow
- Inflammation
- Steatosis
- Centrolobular fibrosis
Transient elastography in chronic liver diseases

- HCV
- HBV
- NAFLD
Hepatitis C

What do we want to know in 2018?

Cirrhosis
Cutoff of liver stiffness for the diagnosis of HCV cirrhosis

- Liver stiffness measurement alone is enough for the diagnosis of cirrhosis

  12 – 14 kPa

- If fibroscan not available, a biomarker can be used.
Hepatitis B

- What do we want to know?
  - Cirrhosis?
  - Treatment needed?
HBV infection

- Hepatitis B Treatment-naive
  - Measurement of liver stiffness (TE)
    - Normal ALT
    - Elevated ALT but <5 x ULN
HBV infection

Hepatitis B Treatment-naive

Measurement of liver stiffness (TE)

Normal ALT

- <6 kPa: No significant fibrosis
- 6-9 kPa: Grey area
- >9 kPa: Severe fibrosis cirrhosis

Elevated ALT but <5 x ULN

- <6 kPa: No significant fibrosis
- 6-12 kPa: Grey area
- >12 kPa: Severe fibrosis cirrhosis

Consider follow-up TE if HBV DNA >2000 IU/ml
Liver biopsy if results influence management
Consider treatment screening for varices and HCC

Exclude other causes of elevated ALT
Whatever HBV DNA level and HBeAg status
Consider follow-up TE
Liver biopsy if results influence management
Consider treatment screening for varices and HCC

J Hepatol 2015;63:237-64
NAFLD. What do we want to screen?
Steatosis? Advanced fibrosis?

NAFL 10-30% → NASH 25-40% → Fibrosis 20-30% → Cirrhosis
Steatosis

Stiffness
- fibrosis

CAP
- steatosis

25 to 65 mm
3 cm³
Steatosis and Controlled Attenuation Parameter

Meta-analysis of individual data on 3,830 patients

The validity of CAP for the diagnosis of fatty liver is lower if the IQR of CAP is ≥40 dB/m.

Karlas et al, JHEP 2017

Wong VW et al, JHEP 2017
CAP in NAFLD patients

N=261 NAFLD patients with Fibroscan + liver biopsy

de Lédinghen V et al. J Gastroenterol Hepatol 2016
## CAP with XL probe

<table>
<thead>
<tr>
<th>Steatosis grade</th>
<th>Probe type</th>
<th>AUROC</th>
<th>p</th>
<th>Cutoff (dB/m)</th>
<th>Se</th>
<th>P</th>
<th>Sp</th>
<th>p</th>
<th>PPV</th>
<th>P</th>
<th>NPV</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>≥ S1 (Pr=48.3 %)</td>
<td>M</td>
<td>0.82 [0.77-0.88]</td>
<td>0.82</td>
<td>246 $\geq$</td>
<td>0.75</td>
<td>1</td>
<td>0.75</td>
<td>1</td>
<td>0.74</td>
<td>1</td>
<td>0.77</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>XL</td>
<td>0.83 [0.77-0.88]</td>
<td></td>
<td>242 $\geq$</td>
<td>0.75</td>
<td>0.75</td>
<td>0.74</td>
<td>0.77</td>
<td>0.76</td>
<td>0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ S2 (Pr=25.9 %)</td>
<td>M</td>
<td>0.89 [0.84-0.93]</td>
<td>0.63</td>
<td>269 $\geq$</td>
<td>0.80</td>
<td>1</td>
<td>0.81</td>
<td>0.85</td>
<td>0.59</td>
<td>0.92</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>XL</td>
<td>0.88 [0.82-0.93]</td>
<td></td>
<td>267 $\geq$</td>
<td>0.80</td>
<td>0.81</td>
<td>0.60</td>
<td>0.92</td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S3 (Pr=15.7 %)</td>
<td>M</td>
<td>0.92 [0.89-0.96]</td>
<td>0.64</td>
<td>285 $\geq$</td>
<td>0.81</td>
<td>0.56</td>
<td>0.81</td>
<td>0.44</td>
<td>0.13</td>
<td>0.96</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>XL</td>
<td>0.93 [0.89-0.97]</td>
<td></td>
<td>286 $\geq$</td>
<td>0.84</td>
<td>0.84</td>
<td>0.50</td>
<td>0.97</td>
<td>0.27</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
MRI-PDFF is better than CAP for fat quantification

Park et al. Gastroenterology 2017
Imajo et al. Gastroenterology 2016
Fibrosis

Stiffness
- fibrosis

CAP
- steatosis
Diagnosis of Fibrosis and Cirrhosis Using Liver Stiffness Measurement in Nonalcoholic Fatty Liver Disease

Vincent Wai-Sun Wong,1,2 Julien Vergniol,3 Grace Lai-Hung Wong,1,2 Juliette Foucher,3 Henry Lik-Yuen Chan,1,2 Brigitte Le Bail,4,5 Paul Cheung-Lung Choi,6 Mathurin Kovo,3 Anthony Wing-Hung Chan,6 Wassil Merrouche,3 Joseph Jao-Yiu Sung,1,2 and Victor de Lédinghen3,4

<table>
<thead>
<tr>
<th>Stage</th>
<th>AUROC</th>
<th>Cutoff (kPa)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥F2</td>
<td>0.84 (0.79-0.90)</td>
<td>5.8</td>
<td>91.1</td>
<td>50.3</td>
<td>56.1</td>
<td>89.0</td>
<td>1.8</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.0</td>
<td>79.2</td>
<td>75.9</td>
<td>69.6</td>
<td>84.0</td>
<td>3.3</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.0</td>
<td>52.5</td>
<td>91.7</td>
<td>81.5</td>
<td>73.5</td>
<td>6.3</td>
<td>0.52</td>
</tr>
<tr>
<td>≥F3</td>
<td>0.93 (0.89-0.96)</td>
<td>7.9</td>
<td>91.1</td>
<td>75.3</td>
<td>52.0</td>
<td>96.6</td>
<td>3.7</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.7</td>
<td>83.9</td>
<td>83.2</td>
<td>59.5</td>
<td>94.6</td>
<td>5.0</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.6</td>
<td>75.0</td>
<td>91.6</td>
<td>72.4</td>
<td>92.6</td>
<td>8.9</td>
<td>0.27</td>
</tr>
<tr>
<td>F4</td>
<td>0.95 (0.91-0.99)</td>
<td>10.3</td>
<td>92.0</td>
<td>87.8</td>
<td>46.0</td>
<td>99.0</td>
<td>7.5</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.3</td>
<td>92.0</td>
<td>87.8</td>
<td>46.0</td>
<td>99.0</td>
<td>7.5</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.5</td>
<td>76.0</td>
<td>91.0</td>
<td>48.7</td>
<td>97.1</td>
<td>8.4</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Liver Stiffness by Transient Elastography and NAFLD

TE has **moderate accuracy** for diagnosis F2-F4 fibrosis (Sens 79%, Spec 75%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cutoff (kPa)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaia 2011</td>
<td>7.0</td>
<td>0.76 [0.58, 0.89]</td>
<td>0.79 [0.64, 0.91]</td>
</tr>
<tr>
<td>Kumar 2013</td>
<td>7.0</td>
<td>0.78 [0.64, 0.88]</td>
<td>0.79 [0.67, 0.88]</td>
</tr>
<tr>
<td>Lupsor 2010</td>
<td>6.8</td>
<td>0.67 [0.41, 0.87]</td>
<td>0.84 [0.71, 0.93]</td>
</tr>
<tr>
<td>Myers 2010</td>
<td>7.7</td>
<td>0.94 [0.71, 1.00]</td>
<td>0.61 [0.42, 0.77]</td>
</tr>
<tr>
<td>Petta 2011</td>
<td>7.25</td>
<td>0.69 [0.57, 0.80]</td>
<td>0.71 [0.59, 0.80]</td>
</tr>
<tr>
<td>Wong 2010</td>
<td>7.0</td>
<td>0.79 [0.70, 0.87]</td>
<td>0.76 [0.68, 0.83]</td>
</tr>
<tr>
<td>Yoneda 2008</td>
<td>6.65</td>
<td>0.88 [0.76, 0.96]</td>
<td>0.74 [0.59, 0.86]</td>
</tr>
</tbody>
</table>

TE has **good accuracy** for diagnosis F3-F4 fibrosis (Sens 85%, Spec 82%)

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<th>Specificity (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Gaia 2011</td>
<td>8.0</td>
<td>0.65 [0.38, 0.86]</td>
<td>0.80 [0.67, 0.90]</td>
</tr>
<tr>
<td>Kumar 2013</td>
<td>9.0</td>
<td>0.85 [0.66, 0.96]</td>
<td>0.88 [0.80, 0.94]</td>
</tr>
<tr>
<td>Lupsor 2010</td>
<td>10.4</td>
<td>1.00 [0.48, 1.00]</td>
<td>0.97 [0.89, 1.00]</td>
</tr>
<tr>
<td>Myers 2010</td>
<td>10.3</td>
<td>0.70 [0.35, 0.93]</td>
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<td>Petta 2011</td>
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<td>0.76 [0.58, 0.89]</td>
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<td>0.84 [0.72, 0.92]</td>
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<td>1.00 [0.69, 1.00]</td>
<td>0.93 [0.81, 0.99]</td>
</tr>
</tbody>
</table>

Kwok et al, APT 2014
Liver Stiffness by Transient Elastography and NAFLD

TE has excellent accuracy for diagnosis F4 fibrosis (Sens 92%, Spec 92%)

Kwok et al, APT 2014
FibroScan M probe and XL probe

PPV advanced fibrosis
71 - 72%

NPV advanced fibrosis
89 - 90%

Wong et al., Am J Gastroenterol 2012; 107:1862–1871
MRE is better than TE for stage of fibrosis in NAFLD

Three single center studies have shown that MRE is better than transient elastography.

*DeLong test used to compare the AUROCs

Park et al. Gastroenterology
Imajo et al. Gastroenterology 2016
Chen et al. Radiology 2016
NAFLD: Fibroscan, SWE or MRE?

AUROC for the diagnosis of advanced fibrosis


13,046 NAFLD subjects
Transient elastography in NAFLD

- CAP is more a « metabolic » parameter than a method to quantify steatosis.

- Transient elastography is a good method to exclude advanced fibrosis and an excellent method to diagnose cirrhosis.

It is enough for clinical practice at bedside.
Transient elastography as screening test?
Patients with insulino-resistance and/or metabolic factors (obesity, diabetes, hypertension, dyslipidemia) should undergo diagnostic procedures for the diagnosis of NAFLD (A1)
In patients with T2DM, the presence of NAFLD should be looked for irrespective of liver enzymes, since T2DM patients are at high risk of disease progression (A2)
Screening diabetic patients for NAFLD

Kwok R et al. Gut 2016;65:1359-68

N = 1800
CAP 222 dB/m
TE 9.6 kPa (M) 9.3 kPa (XL)
Screening diabetic patients for NAFLD
Factors associated with increased LSM

- Longer duration of diabetes
- High BMI
- Increased ALT
- Low HDL cholesterol
- Spot urine albumin/creatinine ratio

Kwok R et al. Gut 2016;65:1359-68
Transient elastography and cirrhosis
Liver stiffness and cirrhosis

Liver stiffness is associated with the severity of cirrhosis

- No OV grade 2/3
- No Child-Pugh B or C
- No ascites
- No HCC
- No OV bleeding

Liver stiffness (in kPa): 15, 27.5, 37.5, 49, 54, 63, 75 kPa

Liver stiffness and advanced chronic liver disease

Stiffness and portal hypertension
Spleen stiffness for oesophageal varices?

Table 5. Diagnostic performance of splenic stiffness measurement by elastography techniques for detecting esophageal varices and large esophageal varices.

<table>
<thead>
<tr>
<th>STUDY, year</th>
<th>Patient (n)</th>
<th>Elastography</th>
<th>CP-C (n)</th>
<th>NAFLD/ALD (n)</th>
<th>Presence of EVs</th>
<th>High-risk EVs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>COV (kPa)</td>
<td>Se (%)</td>
</tr>
<tr>
<td>Calvaruso, 2013 [51]</td>
<td>96</td>
<td>TE</td>
<td>0</td>
<td>0/0</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>Colechìa, 2012 [27]</td>
<td>100</td>
<td>TE</td>
<td>0</td>
<td>0/0</td>
<td>41.3 a</td>
<td>98</td>
</tr>
<tr>
<td>Fraquelli, 2014 [79]</td>
<td>198</td>
<td>TE</td>
<td>–</td>
<td>0/0</td>
<td>65</td>
<td>91</td>
</tr>
<tr>
<td>Sharma, 2013 [41]</td>
<td>174</td>
<td>TE</td>
<td>20</td>
<td>–/77</td>
<td>40.8</td>
<td>94</td>
</tr>
<tr>
<td>Stefanescu, 2011 [53]</td>
<td>191</td>
<td>TE</td>
<td>13</td>
<td>–/–</td>
<td>46.4</td>
<td>84</td>
</tr>
<tr>
<td>Wong, 2016 [80]</td>
<td>144</td>
<td>TE</td>
<td>–</td>
<td>0/0</td>
<td>21.4 a</td>
<td>90</td>
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<tr>
<td>Kim, 2015 [81]</td>
<td>125</td>
<td>ARFI</td>
<td>8</td>
<td>–/41</td>
<td>3.16 c</td>
<td>87</td>
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<td>Rizzo, 2014 [82]</td>
<td>54</td>
<td>ARFI</td>
<td>0</td>
<td>0/0</td>
<td>3.1 c</td>
<td>96</td>
</tr>
</tbody>
</table>

TE: transient elastography; NAFLD: Nonalcoholic fatty liver disease; ALD: alcoholic liver disease; Se: sensitivity; Sp: specificity; COV: cutoff value; CP-C: Child–Pugh C; EVs: esophageal varices.

a: Rule-out cutoff value.
b: Rule-in cutoff value.
c: m/s.
Non-invasive diagnosis of oesophageal varices

Fibroscan

Liver stiffness > 20 kPa OR Platelet count < 150,000 → OGD

Liver stiffness < 20 kPa AND Platelet count > 150,000 → Repeat annually

cAFLD

Platelet count

Pragmatic use of liver stiffness
Liver stiffness is associated with the risk of hepatocellular carcinoma

- 866 patients with HCV infection, 3-year follow up
- Hepatocellular carcinoma during follow-up: 77

![Graph showing cumulative incidence of hepatocellular carcinoma over years after enrollment for different liver stiffness modulus (LSM) levels.](graph.png)
Liver stiffness is associated with overall survival

1457 HCV patients; Follow-up: 5 years
Overall survival: 91.7%

Conclusion
Transient elastography in clinical practice

- <6 kPa HBV
- 8-10 kPa NAFLD
- < 10 kPa No ACLD
- 12-14 kPa HCV
- 20 kPa Varices

- 9 kPa HBV nALT
- 12 kPa HBV ALT
- 15 kPa ACLD
Transient elastography: the future

- Screening general population or specific populations

- Follow-up of patients
  - Treated HBV or SVR HCV patients
  - NASH with specific treatments
  - Prediction of NAFLD patients at risk of cirrhosis or HCC
  - Prediction of CV risks in NAFLD patients

- Spleen stiffness?
Thanks

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