Welcome

The CLDF would like to thank our supporter, Bristol Myers Squibb, for providing an educational grant for this initiative.
Imaging and Biomarkers in HCC: Diagnosis and Surveillance
HCC Surveillance Goals and Outcomes

- Early tumor detection
- Implementation of curative treatments
- Increase overall survival among patients with cirrhosis
- Decreased mortality

Practical Considerations: Surveillance and Diagnostic Evaluation

- If good-quality US is available, AFP may not confer substantial incremental benefit
- If not sure about US quality or when dealing with patients at risk for surveillance failure, order HCC biomarkers

AFP=alpha-fetoprotein; CT=computerized tomography; MRI=magnetic resonance imaging; US=ultrasound.

### Major Guidelines Recognize the Importance of Routine Surveillance in High-risk Populations

<table>
<thead>
<tr>
<th>Society/Institution</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASLD&lt;sup&gt;1&lt;/sup&gt;</td>
<td>US every 6 months</td>
</tr>
<tr>
<td>American Association for the Study of Liver Diseases</td>
<td></td>
</tr>
<tr>
<td>EASL&lt;sup&gt;2&lt;/sup&gt;</td>
<td>US every 6 months</td>
</tr>
<tr>
<td>European Association for the Study of the Liver</td>
<td></td>
</tr>
<tr>
<td>APASL&lt;sup&gt;3&lt;/sup&gt;</td>
<td>AFP + US every 6 months</td>
</tr>
<tr>
<td>Asian-Pacific Association for the Study of the Liver</td>
<td></td>
</tr>
<tr>
<td>NCCN&lt;sup&gt;4&lt;/sup&gt;</td>
<td>AFP + US every 6-12 months</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td></td>
</tr>
<tr>
<td>VA&lt;sup&gt;5&lt;/sup&gt;</td>
<td>AFP + US every 6-12 months</td>
</tr>
<tr>
<td>United States Department of Veterans Affairs</td>
<td></td>
</tr>
<tr>
<td>JSH-HCC&lt;sup&gt;6&lt;/sup&gt;</td>
<td>High-risk: US every 6 months + AFP/DCP/AFP-L3 every 6 months</td>
</tr>
<tr>
<td>Japan Society of Hepatology</td>
<td>Very High-risk: US every 6 months + AFP/DCP/AFP-L3 every 6 months + CT/MRI (optional) every 6-12 months</td>
</tr>
</tbody>
</table>

AFP=alpha-fetoprotein; AFP-L3=\textit{Lens culinaris} agglutinin-reactive fraction of AFP; CT=computerized tomography; DCP=des-y-carboxyprothrombin; MRI=magnetic resonance imaging; US=ultrasound.

Surveillance and Diagnostic Tests

- **Serologic markers**
  - Alpha-fetoprotein (AFP)
  - AFP-L3%
  - Des-gamma carboxyprothrombin (DCP)

- **Imaging**
  - Ultrasound
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI)

*Must be multiphase with contrast*
How to Conduct Surveillance?  
α-Fetoprotein May Add Value to Ultrasound

- HCC can produce AFP values ranging from normal to >100,000 ng/mL\(^1\)
  - No correlation with stage or size of tumor
- Limitations of AFP alone\(^2\):
  - Often increased in patients with chronic liver disease in the absence of cancer
  - May be elevated in patients with HCC, embryonic carcinomas, gastric cancer, and lung cancer

AFP is inadequate as a marker for “diagnosis” of HCC in the absence of ultrasound and subsequent CT or MR imaging.

AFP=alpha fetoprotein; CT=computerized tomography; MRI=magnetic resonance imaging.
**Alpha-Fetoprotein**

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Positive DLR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.9 ng/mL (normal)</td>
<td>0.62</td>
<td>0.80</td>
<td>0.30</td>
<td>0.94</td>
<td>3.04</td>
</tr>
<tr>
<td>50 ng/mL</td>
<td>0.31</td>
<td>0.96</td>
<td>0.55</td>
<td>0.91</td>
<td>8.72</td>
</tr>
<tr>
<td>100 ng/mL</td>
<td>0.26</td>
<td>0.98</td>
<td>0.69</td>
<td>0.90</td>
<td>16.03</td>
</tr>
<tr>
<td>200 ng/mL</td>
<td>0.20</td>
<td>&gt;0.99</td>
<td>0.79</td>
<td>0.90</td>
<td>26.20</td>
</tr>
<tr>
<td>400 ng/mL</td>
<td>0.15</td>
<td>&gt;0.99</td>
<td>0.81</td>
<td>0.89</td>
<td>31.05</td>
</tr>
<tr>
<td>1000 ng/mL</td>
<td>0.13</td>
<td>&gt;0.99</td>
<td>0.94</td>
<td>0.89</td>
<td>113.54</td>
</tr>
</tbody>
</table>

DLR, diagnostic likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

*Positive DLR is defined as: sensitivity/(1-specificity) and it represents the odds ratio that an elevated alpha fetoprotein result will be observed in an hepatocellular carcinoma (HCC) patient compared to a patient without HCC. Thus, tests with higher positive DLR values are more useful.

## Progressive Rise of AFP Over Time

<table>
<thead>
<tr>
<th>aFP</th>
<th>HCC Prevalence (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥200 ng/ml</td>
<td>10</td>
<td>97.58</td>
<td>93.4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>95.03</td>
<td>96.7</td>
</tr>
<tr>
<td>≥400 ng/ml</td>
<td>10</td>
<td>95.7</td>
<td>91.86</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>91.4</td>
<td>95.97</td>
</tr>
<tr>
<td>Elevation ≥7 ng/ml/month</td>
<td>10</td>
<td>98.7</td>
<td>96.92</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>97.4</td>
<td>98.52</td>
</tr>
</tbody>
</table>

HCC Surveillance Biomarker: Alpha-Fetoprotein-L3 (AFP-L3)

- AFP-L3 is a fucosylated isoform of AFP.
- AFP-L3 binds to lectin Lens culinaris (lentil) agglutinin (LCA) which interacts with AFP-L3 but not AFP-L1 (majority of AFP).
- Relevance of AFP-L3 to HCC:
  - AFP-L3 has been shown to be elevated in patients with HCC. Elevation of L3 occurs early in HCC
  - AFP-L3 (%) is highly specific for HCC

\[
\text{AFP-L3} \, (\%) = \frac{\text{AFP-L3} \, (\text{ng/mL})}{\text{Total AFP} \, (\text{ng/mL})} \times 100
\]

\textit{Cut-off Point: 10\% (Intended Use)}

HCC Surveillance Biomarker: Des-gamma-Carboxy Prothrombin (DCP)

- Normal hepatocytes post-translationally carboxylate prothrombin precursors before secretion.
- DCP is a secreted non-carboxylated immature form of prothrombin.
- Unconverted glutamic acid residues are due to an absence in many HCC of vit. K dependent carboxylase.
- aka PIVKA-II (proteins induced by vitamin K absence or antagonist-II).
  - *The carboxylation defect is also in vitamin K deficiency (also warfarin use)*

Cut-off Point: 7.5 ng/mL

# Inclusion of AFP-L3 & DCP Improves Early Detection

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Tool</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colli et al (2006)¹</td>
<td>Ultrasound</td>
<td>60%</td>
<td>97%</td>
<td>“Ultrasound is…insufficiently sensitive to detect HCC in many cirrhotics or to support an effective surveillance program.”</td>
</tr>
<tr>
<td>Singal et al (2012)²</td>
<td>Ultrasound</td>
<td>43.9%</td>
<td>91.5%</td>
<td>Ultrasound is suboptimal when used alone</td>
</tr>
<tr>
<td>Volk et al (2007)³</td>
<td>AFP, AFP-L3 &amp; DCP</td>
<td>88%</td>
<td>91%</td>
<td>Combined use of AFP, AFP-L3 and DCP results in good detection of HCC with minimal false positives</td>
</tr>
<tr>
<td>Hann et al (2013)⁴</td>
<td>AFP, AFP-L3 &amp; DCP</td>
<td>83%</td>
<td>&gt;90%</td>
<td></td>
</tr>
</tbody>
</table>

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The GALAD Model: Combined Use of Clinical Features and HCC Biomarkers to Predict HCC Risk

\[
Z = -10.08 + 1.67 \times \text{[Gender/Sex]} + 0.09 \times \text{[Age]} + 0.04 \times \text{[AFP-L3]} \\
+ 2.34 \times \log \text{[AFP]} + 1.33 \times \log \text{[DCP]}
\]

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \beta ) (se)</th>
<th>Odds Ratio (95% CI)</th>
<th>( \chi^2 )</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-10.08 (1.08)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>0.09 (0.01)</td>
<td>1.10 (1.07-1.13)</td>
<td>44.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>1.67 (0.33)</td>
<td>5.30 (2.79-10.07)</td>
<td>25.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log (AFP)</td>
<td>2.34 (0.33)</td>
<td>10.34 (5.40-19.79)</td>
<td>49.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AFP-L3</td>
<td>0.04 (0.01)</td>
<td>1.04 (1.01-1.07)</td>
<td>8.66</td>
<td>0.003</td>
</tr>
<tr>
<td>Log (DCP)</td>
<td>1.33 (0.17)</td>
<td>3.77 (2.73-5.21)</td>
<td>64.56</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Sex = 1 (Males) or 0 (Females)

GALAD Score Improves AUROC Compared to Biomarkers Alone

http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/galad
Surveillance and Diagnostic Tests

• Serologic markers
  – Alpha-fetoprotein (AFP)
  – AFP-L3%
  – Des-gamma carboxyprothrombin (DCP)

• Imaging
  – Ultrasound
  – Computed tomography (CT)
  – Magnetic resonance imaging (MRI)

Must be multiphase with contrast
Ultrasound (US) in Surveillance

- Excellent specificity (>90%), but low sensitivity – a meta-analysis indicates US sensitivity in detecting early stage HCC may be as low as 63%

- Multiple limitations
  - Does not detect infiltrative disease
  - Sensitivity decreased in difficult patients
    - Cirrhotic nodular livers
    - Obesity
    - Abdominal gas
    - Noncompliant with breath-hold
    - Ascites
    - NASH
  - Highly operator dependent, time

- Real-life US sensitivity likely much lower than that of studies

Predictors of Ultrasound Failure

- Retrospective study of 1170 patients evaluated causes of failure of US:
  - HCC was found beyond Milan criteria in 32.2% of patients surveilled semi-annually with US
  - Single HCCs ≤2 cm were detected in only 20% of cases
- Nearly half of failures were associated with aggressive HCC
- Increased risk of failure of HCC detection in:
  - Men
  - BMI >25
  - Child-Pugh B
  - AFP >200 ng/mL

Surveillance and Diagnostic Tests

- **Serologic markers**
  - Alpha-fetoprotein (AFP)
  - AFP-L3%
  - Des-gamma carboxyprothrombin (DCP)

- **Imaging**
  - Ultrasound
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI)

Must be multiphase with contrast
Scans and Biopsies

• Scans: *which ones?*
  – US is used for ease and cost, but sensitivity is low\(^1\)
  – Triple-phase helical CT or triple-phase dynamic contrast enhanced MRI is more sensitive\(^2\)
    • Presence of arterial enhancement followed by washout has sensitivity (90%) and specificity (95%)\(^3\)

• When to biopsy and when NOT to biopsy
  – 95% specific for HCC: biopsy NOT needed in most patients\(^3\)
  – Only focal hepatic mass with atypical imaging findings or focal hepatic mass detected in a non-cirrhotic liver should undergo biopsy\(^3\)

Triple Phase Imaging
HCC Diagnosis
Following Detection of Mass in Cirrhotic Liver

- **<1 cm**
  - Repeat imaging q 3 m (CT/MRI/US)

- **>1 cm**
  - 1 imaging techniques (4 phase CT/dynamic MRI)
    - Typical: enhanced study (CT or MRI) AND arterial hypervascularity AND portal venous or delayed washout
    - Atypical
      - Other contrast enhanced study (CT or MRI)

- Stable 18-24 m
  - Resume standard surveillance (q 6-12 m)

- Enlarging
  - Proceed based on lesion size

VASCULAR PATTERN

- Typical
  - Repeat biopsy or Imaging f/u
  - Change in size or profile
  - Repeat imaging and/or biopsy

- Atypical
  - Treat as HCC

Bruix and Sherman. AASLD guidelines. 2010
CT vs MRI

- Meta-analysis of 40 studies on CT or MRI imaging, total of 1135 patients with CT and 2489 patients with MRI

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>MRI (all)</th>
<th>MRI with Eovist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-patient sensitivity</td>
<td>83%</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Per patient specificity</td>
<td>81%</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Per lesion sensitivity</td>
<td>72%</td>
<td>79%</td>
<td>87%</td>
</tr>
</tbody>
</table>

### Sensitivity of Ultrasound Alone for Early HCC

**Pooled Sensitivity**

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Sensitivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.21 (0.05 – 0.51)</td>
<td></td>
</tr>
<tr>
<td>0.33 (0.04 – 0.78)</td>
<td></td>
</tr>
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</tr>
<tr>
<td>0.67 (0.22 – 0.96)</td>
<td></td>
</tr>
<tr>
<td>0.82 (0.70 – 0.91)</td>
<td></td>
</tr>
<tr>
<td>0.25 (0.03 – 0.65)</td>
<td></td>
</tr>
<tr>
<td>0.24 (0.17 – 0.33)</td>
<td></td>
</tr>
<tr>
<td>0.44 (0.14 – 0.79)</td>
<td></td>
</tr>
<tr>
<td>0.36 (0.21 – 0.53)</td>
<td></td>
</tr>
<tr>
<td>0.68 (0.45 – 0.86)</td>
<td></td>
</tr>
<tr>
<td>0.65 (0.56 – 0.73)</td>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td>0.56 (0.21 – 0.86)</td>
<td></td>
</tr>
<tr>
<td>0.89 (0.52 – 1.00)</td>
<td></td>
</tr>
<tr>
<td>0.26 (0.14 – 0.41)</td>
<td></td>
</tr>
</tbody>
</table>

**Sensitivity Cutoffs**

- **< 50% sensitivity**
- **> 50% sensitivity**

**Studies**

- Pateron 1994
- Larcos 1998
- Tradati 1998
- Henrion 2000
- Bolondi 2001
- Santagostino 2003
- Sangiovanni 2004
- Paul 2007
- Lok 2010
- Qian 2010
- Trinchet 2011
- Singal 2012
- Pocha 2013
- Frey 2015
- Kim 2016

**Pooled Sensitivity**

- 0.47 (0.33 – 0.61)

Singal, ILCA 2018
Meta-Analysis: Sensitivity of Ultrasound +/- AFP for Early HCC

Benefits of AFP consistent across subgroups

- Prospective studies:
  RR 0.78 (0.66 – 0.92)
- Studies in United States:
  RR 0.59 (0.41 – 0.85)
- Cirrhosis-only studies:
  RR 0.76 (0.60 – 0.95)
- Studies after 2000:
  RR 0.79 (0.66 – 0.95)

Sensitivity ultrasound 45% (30-62%) vs. US+AFP: 63% (48-75%)

Singal, ILCA 2018
Conclusions

- HCC is a rapidly rising cause of liver-related death in the United States
- Screening and surveillance for liver cancer saves lives and is cost effective
- Multiple organizations recommend HCC screening in high risk patients
- Understanding the strengths and weaknesses of the available screening methods will help to ensure early diagnosis in patients at risk
Meta-Analysis: Sensitivity of Ultrasound Alone for Early HCC

15 studies
1994 – 2016

Author Year
- Pateron 1994
- Larcos 1998
- Tradati 1998
- Henrion 2000
- Bolondi 2001
- Santagostino 2003
- Sangiovanni 2004
- Paul 2007
- Lok 2010
- Qian 2010
- Trinchet 2011
- Singal 2012
- Pocha 2013
- Frey 2015
- Kim 2016

Sensitivity (95% CI)
- 0.21 (0.05 – 0.51)
- 0.33 (0.04 – 0.78)
- 0.33 (0.04 – 0.78)
- 0.67 (0.22 – 0.96)
- 0.82 (0.70 – 0.91)
- 0.25 (0.03 – 0.65)
- 0.24 (0.17 – 0.33)
- 0.44 (0.14 – 0.79)
- 0.36 (0.21 – 0.53)
- 0.68 (0.45 – 0.86)
- 0.65 (0.56 – 0.73)
- 0.32 (0.18 – 0.48)
- 0.56 (0.21 – 0.86)
- 0.89 (0.52 – 1.00)
- 0.26 (0.14 – 0.41)

Pooled

< 50% sensitivity
> 50% sensitivity

Singal, ILCA 2018
Meta-Analysis: Sensitivity of Ultrasound +/- AFP for Early HCC

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Singal, ILCA 2018
Thank you!