Improved Liver Cancer Surveillance with Serum Biomarkers AFP-L3 & DCP

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This webinar will:

• Review the epidemiology of HCC
• Summarize staging and curative treatment options
• Describe in detail the available biomarkers for early detection of HCC and their application
Learning Objectives

• Identify patients at risk for HCC
• Understand the importance of early detection of HCC
• Be able to describe and apply the available serum biomarkers for HCC
Pre-Questions

• How does efficacy vs effectiveness apply to HCC screening?
• What processes could laboratories implement to aid early diagnosis of HCC?
• What role do biomarkers play in determining response to treatment and/or recurrence of HCC?
HCC Epidemiology

- 3rd leading cause of cancer mortality worldwide
- 10th leading in US
- Almost exclusively presents in patients with chronic liver disease
HCC Epidemiology

Worldwide Incidence of Hepatocellular Carcinoma

- High (> 30:100,000)
- Intermediate (3-30:100,000)
- Low or data unavailable (< 3:100,000)

El-Serag HB, Gastroenterology 2004
Incidence by State
HCC Epidemiology

Viral Hepatitis causes most HCC in the United States

- HCV: 47%
- HBV: 15%
- Both: 5%
- Neither: 33%
Non-Alcoholic Fatty Liver Disease
A rising cause of HCC

Steatosis

Steatohepatitis

Cirrhosis

Hepatocellular carcinoma

Steatosis

Steatohepatitis

Non-Alcoholic Fatty Liver Disease
A rising cause of HCC

Steatosis

Steatohepatitis

Cirrhosis

Hepatocellular carcinoma
Epidemiology Summary

- HCC is more common than people realize
- Most HCC occurs in patients with underlying liver disease
Diagnosis and Management Overview
HCC Diagnosis

Dual Blood Supply of Liver

- Vascular supply of HCC arises from the hepatic artery through neovascularization.
- Triple phase contrast imaging is key

Triple Phase Imaging in HCC

Arterial phase

2-min delayed

Arterial phase

5-min delayed
LI-RADS

- Classification system for imaging diagnosis of HCC:
  - 1,2: not HCC
  - 3: indeterminate
  - 4: suspicious
  - 5: diagnostic
Prognosis by BCLC Stage

Marrero JA, et al, Hepatology 2005
BCLC Stage A

Early HCC (potential cure)

• Resection
  o 1 tumor <5 cm, no portal hypertension

• Ablation
  o 1 tumor <3 cm

• Transplant
  o Milan criteria: 1 tumor 2-5 cm, 3 <3 cm, no macrovascular invasion
Barcelona Management Strategy

HCC

PS 0, CP A

PS 0-2, CP A-B

PS > 2, CP C

not txp candidate

0
Very Early

A
Early Milan

B
Intermediate Multinodular

C
Advanced PVT, N1, M1

D
Terminal Any N, M

Single

3 nodules ≤ 3 cm

Portal HTN, bilirubin

Elevated CoMorb

Normal No Yes

Resection Transplant Ablation/XRT TACE/Y90 Chemo Symptomatic
Diagnosis and Management Summary

• Diagnosis of HCC is usually by triple-phase CT/MRI
  o Biopsy needed <10% of time
• Management is guided by stage
• Curative treatment depends on early diagnosis!
Screening and Surveillance

• **Screening**: Application of diagnostic tests, imaging or procedures in apparently healthy patients

• **Surveillance**: Serial application of blood-based tests, imaging or procedures in an at-risk patient population
Surveillance for HCC Reduces Mortality:
A Randomized Controlled Trial

Changes in Survival in Japan Since Inception of Surveillance

![Graph showing survival rates in different periods]

**Table:**

<table>
<thead>
<tr>
<th>Period</th>
<th>N</th>
<th>Median survival in months</th>
<th>% screened</th>
<th>Median age (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966 – 1980</td>
<td>178</td>
<td><strong>2.96 (2.4 – 3.4)</strong></td>
<td>15.23 (n=151)</td>
<td>60 (54 – 67)</td>
</tr>
<tr>
<td>1991 – 2000</td>
<td>812</td>
<td>27.5 (25.8 – 31.1)</td>
<td>72.41 (n=812)</td>
<td>64 (59 – 70)</td>
</tr>
<tr>
<td>2001 – 2013</td>
<td>1105</td>
<td>52.2 (44.1 – 59.7)</td>
<td>76.80 (n=1103)</td>
<td>70 (63 – 76)</td>
</tr>
</tbody>
</table>

*Pre-surveillance*

*Ikai I et al, Hepatol Res. (2010)*
### Guidelines for HCC Surveillance

<table>
<thead>
<tr>
<th>Institutions</th>
<th>Guidelines</th>
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<tbody>
<tr>
<td><strong>AASLD</strong> American Association for the Study of Liver Diseases</td>
<td>US, every 6 months +/- AFP</td>
</tr>
<tr>
<td><strong>NCCN</strong> National Comprehensive Cancer Network</td>
<td>AFP + US every 6-12 months</td>
</tr>
<tr>
<td><strong>EASL</strong> European Association for the Study of the Liver</td>
<td>US, every 6 months</td>
</tr>
<tr>
<td><strong>APASL</strong> Asian-Pacific Association for the Study of the Liver</td>
<td>AFP + US, every 6 months</td>
</tr>
<tr>
<td><strong>JSH</strong> Japan Society of Hepatology</td>
<td>AFP + AFP-L3 + DCP + US, 6 months for high risk (3-4 months after treatment, 2013)</td>
</tr>
</tbody>
</table>

**NOTE:** Jan 2019 AASLD HCC surveillance guidance mentions AFP-L3%, DCP and GALAD as potential enhancements.
Efficacy vs Effectiveness

• Variable completion rate

• Operator dependent: > half of the patients enrolled in surveillance programs receive a suboptimal quality ultrasound
  - Excellent 13/154 (8.4%)
  - Good 44/154 (28.6%)
  - Fair 44/154 (28.6%)
  - Poor 53/154 (34.4%)

HCC Surveillance Biomarker:
Alpha-fetoprotein (AFP)

• AFP is a glycoprotein produced by:
  o Normal fetal hepatocytes
  o Normal regenerating hepatocytes
  o Most (not all HCCs)
  o Inflammation

• Low overall sensitivity and specificity for HCC
• Better performance when levels are exponentially rising (trending up) or fluctuating

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).
- **AFP-L3%** is FDA cleared for HCC risk assessment.
- Measured as percentage of the overall AFP, not linked to absolute amount **AFP-L3**.

HCC Surveillance Biomarker

**AFP-L3 Alpha-fetoprotein L3**

**AFP-L3%**: expressed as a % of the ratio of AFP-L3 to total AFP

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

**Threshold**: 10% (Intended Use)
des-gamma-carboxy prothrombin: DCP

- Normal hepatocytes post-translationally carboxylate prothrombin precursors before secretion.
- **DCP** is a secreted non-carboxylated immature form of prothrombin.
  - aka PIVKA-II (proteins induced by vitamin K absence or antagonist-II)
- Unconverted glutamic acid residues are due to an absence in many HCC cells of vit. K dependent carboxylase.
- **DCP** is FDA cleared for HCC risk assessment.

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**Cut-off Point:** 7.5 ng/mL

1 ng/mL = 52.6 mAU/mL
des-gamma-carboxy prothrombin: DCP

1 ng/mL = 52.6 mAU/mL
A Statistical Model (GALAD):
A Combination of AFP, AFP-L3 & DCP with Age and Gender

The model predicts HCC presence in patients with chronic liver disease:

$$Z = -10.32 + 0.10 \times \text{Age} + 1.39 \times \text{Gender} + 2.43 \times \log(\text{AFP}) + 0.040 \times \text{AFP-L3} + 1.45 \times \log(\text{DCP})$$

From the calculated value of $Z$, the probability of HCC in a patient with chronic liver disease (ranging from 0 to 1) is calculated by:

$$\text{GPr}(\text{HCC}) = \frac{\exp(Z)}{1+\exp(Z)}$$

Johnson et al, Cancer Epi Biom and Prev 2014
Added Value of The GALAD Model

- GALAD AUROC 0.97
- log(AFP) AUROC 0.88
- AFP-L3 AUROC 0.84
- log(DCP) AUROC 0.90
Roles for Biomarkers

• Early detection (screening/surveillance)
• Prognosis
• Evaluate for recurrence
What role does the lab play?

- Implement the GALAD model
- Flag rising values
- Linkage to care
Questions?