Recommendations to Optimize Surveillance of HCC

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Upon completion of this activity, the participants should be better able to:

- Explain data on the prevalence and consequences of HCC
- Demonstrate strategies to incorporate classification, diagnostic and treatment updates into clinical practice to individualize treatment strategies
- Analyze recently approved and emerging treatment options and understand how new agents are improving the standard of care for all HCC patients
Hepatocellular Carcinoma Is 4th Leading Cause of Cancer-Related Death Worldwide
HCC-Related Morality Is Increasing in the United States

Top 15 causes of cancer death in the United States, 2010-2014:

- Lung: -2.5%
- Colon & rectum: -2.5%
- Breast: -1.9%
- Pancreas: +0.1%
- Prostate: -0.9%
- Leukemia: -2.6%
- Lymphoma: -2.3%
- Bladder: +0.4%
- Brain: +2.7%
- Esophagus: -1.1%
- Ovary: -2.5%
- Kidney: -1.1%
- Myeloma: -0.8%
- Stomach: -0.6%
- Myeloma: -2.3%

Data from http://seer.cancer.gov
Most HCC in the United States Occur in the Setting of Cirrhosis

Nonalcoholic steatohepatitis
Alcohol-related liver disease
Hepatitis B viral infection
Hepatitis C viral infection

Normal liver → Chronic inflammation → Chronic hepatitis → Cirrhosis → HCC
DAA-Based Sustained Viral Response Reduces but Does Not Eliminate HCC Risk in Hepatitis C Cirrhosis

Many NASH HCC Patients Do Not Have Cirrhosis

Very high probability non-cirrhotic: Histology and no features on imaging
High probability non-cirrhotic: APRI <1; no features on imaging; NL albumin, plt, INR

HCC Risk in Patients With NASH Restricted to Those With Cirrhosis

N= 4235 cirrhosis; 292,366 no cirrhosis

1.06 per 100 patient-years

0.008 per 100 patient-years

### Professional Society Guidelines Recommend HCC Surveillance in High-Risk Individuals Including Those With Cirrhosis

#### Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Threshold Incidence for Efficacy of Surveillance (&gt;0.25 LYG; % per year)</th>
<th>Incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surveillance benefit</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian male hepatitis B carriers over age 40</td>
<td>0.2</td>
<td>0.4%-0.6% per year</td>
</tr>
<tr>
<td>Asian female hepatitis B carriers over age 50</td>
<td>0.2</td>
<td>0.3%-0.6% per year</td>
</tr>
<tr>
<td>Hepatitis B carrier with family history of HCC</td>
<td>0.2</td>
<td>Incidence higher than without family history</td>
</tr>
<tr>
<td>African and/or North American blacks with hepatitis B</td>
<td>0.2</td>
<td>HCC occurs at a younger age</td>
</tr>
<tr>
<td>Hepatitis B carriers with cirrhosis</td>
<td>0.2-1.5</td>
<td>3%-8% per year</td>
</tr>
<tr>
<td>Hepatitis C cirrhosis</td>
<td>1.5</td>
<td>3%-5% per year</td>
</tr>
<tr>
<td>Stage 4 PBC</td>
<td>1.5</td>
<td>3%-5% per year</td>
</tr>
<tr>
<td>Genetic hemochromatosis and cirrhosis</td>
<td>1.5</td>
<td>Unknown, but probably &gt;1.5% per year</td>
</tr>
<tr>
<td>Alpha-1 antitrypsin deficiency and cirrhosis</td>
<td>1.5</td>
<td>Unknown, but probably &gt;1.5% per year</td>
</tr>
<tr>
<td>Other cirrhosis</td>
<td>1.5</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Surveillance benefit uncertain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B carriers younger than 40 (males) or 50 (females)</td>
<td>0.2</td>
<td>&lt;0.2 per year</td>
</tr>
<tr>
<td>Hepatitis C and stage 3 fibrosis</td>
<td>1.5</td>
<td>&lt;1.5% per year</td>
</tr>
<tr>
<td>NAFLD without cirrhosis</td>
<td>1.5</td>
<td>&lt;1.5% per year</td>
</tr>
</tbody>
</table>

Abdominal Ultrasound +/- Serum Biomarker, Alpha Fetoprotein, Are Recommended Surveillance Tests
Surveillance Should Be Performed at Semi-Annual Intervals

<table>
<thead>
<tr>
<th>Variable</th>
<th>3-month Surveillance (n=640)</th>
<th>6-month Surveillance (n=638)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal lesion &lt;1 cm</td>
<td>73 (41%)</td>
<td>43 (28%)</td>
</tr>
<tr>
<td>Focal lesion 1-2 cm</td>
<td>71 (40%)</td>
<td>78 (50%)</td>
</tr>
<tr>
<td>HCC development Less than 2 cm Within Milan</td>
<td>53 (28%) 20 (38%) 42 (79%)</td>
<td>70 (42%) 29 (41%) 50 (71%)</td>
</tr>
</tbody>
</table>

There Are Established Recall Procedures for Surveillance Test Results
HCC Diagnosis Can Be Established Non-Invasively Based on Imaging Alone

Arterial phase

Delayed phase
# LI-RADS Criteria for HCC Diagnosis

<table>
<thead>
<tr>
<th>LI-RADS Category</th>
<th>Concept and Definition</th>
</tr>
</thead>
</table>
| LR-1 Definitely Benign | **Concept:** 100% certainty observation is benign.  
**Definition:** Observation with imaging features diagnostic of a benign entity, or definite disappearance at follow up in absence of treatment. |
| LR-2 Probably Benign | **Concept:** High probability observation is benign.  
**Definition:** Observation with imaging features suggestive but not diagnostic of a benign entity. |
| LR-3 Intermediate probability for HCC | **Concept:** Both HCC and benign entity have moderate probability.  
**Definition:** Observation that does not meet criteria for other LI-RADS categories. |
| LR-4 Probably HCC | **Concept:** High probability observation is HCC but there is not 100% certainty.  
**Definition:** Observation with imaging features suggestive but not diagnostic of HCC. |
| LR-5 Definitely HCC | **Concept:** 100% certainty observation is HCC.  
**Definition:** Observation with imaging features diagnostic of HCC or proven to be HCC at histology. |
| LR-M Probable malignancy, not specific for HCC | **Concept:** High probability that observation is a malignancy, but imaging features are not specific for HCC.  
**Definition:** Observation with one or more imaging features that favor non-HCC malignancy. |
| LR-Treated Treated Observation | **Concept:** Loco-regionally treated observation.  
**Definition:** Observation that has undergone loco-regional treatment |
Biopsy Still Plays a Role in HCC Diagnosis
HCC Surveillance Reduces Mortality in Patients With Chronic Hepatitis B


<table>
<thead>
<tr>
<th>Variable</th>
<th>Screen Group (n=9373)</th>
<th>Control Group (n=9443)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC cases</td>
<td>86</td>
<td>67</td>
</tr>
<tr>
<td>% Stage I</td>
<td>60.5%</td>
<td>0%</td>
</tr>
<tr>
<td>% Curative treatment</td>
<td>46.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td># HCC death</td>
<td>32</td>
<td>54</td>
</tr>
<tr>
<td>Mortality (per 100,000)</td>
<td>83.2</td>
<td>131.5</td>
</tr>
<tr>
<td>Rate Ratio</td>
<td>0.63 (0.4-0.9)</td>
<td></td>
</tr>
</tbody>
</table>
HCC Surveillance Associated With Early Detection and Improved Survival in Patients With Cirrhosis

Identified 47 studies with 15,158 patients – 6284 (41.4%) detected by surveillance

Surveillance associated with:

- Early detection OR 2.8, 95% CI 1.80 – 2.37
- Curative treatment: OR 2.24, 95%CI 1.99 – 2.52
- Improved survival OR 1.90, 95%CI 1.67 – 2.17

Survival benefit persisted in studies adjusting for lead time bias

Potential Interventions to Improving Surveillance Effectiveness and Reducing HCC Morality

**Increasing surveillance rates**

**Promoting education**
- Patient education
- Practitioner training
- Enlisting of primary care providers

**Improving compliance**
- Systems-level interventions
- Dedicated clinical pathways
- Clinical reminder systems
- Navigation programmes
- Mailed outreach

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**Refinement of screening strategies**

<table>
<thead>
<tr>
<th>Predictive biomarkers</th>
<th>Machine learning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low HCC risk</td>
<td>Moderate/High HCC risk</td>
</tr>
</tbody>
</table>

**Screening using contrast-enhanced imaging**

**Early diagnosis biomarkers**

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Potential Interventions to Improving Surveillance Effectiveness and Reducing HCC Morality

- Increasing surveillance rates
- Refinement of screening strategies
- Predictive biomarkers
- Machine learning
- Promoting education
  - Patient education
  - Practitioner training
  - Enlisting of primary care providers
- Improving compliance
  - Systems-level interventions
  - Dedicated clinical pathways
  - Clinical reminder systems
  - Navigation programmes
  - Mailed outreach
- Risk stratification
- Low HCC risk
- Moderate/High HCC risk
- Screening using contrast-enhanced imaging
  + Early diagnosis biomarkers

Ultrasound Alone Has Poor Sensitivity for Early HCC Detection

CT Is Not Viable Option for HCC Screening Given Potential Harms

More expensive

Ionizing radiation

Nephrotoxicity?
MRI Is More Sensitive for Early Tumor Detection but May Be Limited by Cost Effectiveness

- Prospective study with 407 Child A-B patients (majority HBV-infected)
  - 1112 surveillance round over 1.5 years
  - Semi-annual ultrasound and MRI done in all patients
- 43 patients diagnosed with HCC
  - 32 very early stage and 10 early stage HCC

<table>
<thead>
<tr>
<th>Cohort</th>
<th>MRI</th>
<th>US</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>86%</td>
<td>28%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Sensitivity for BCLC 0</td>
<td>86%</td>
<td>26%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Specificity</td>
<td>97%</td>
<td>94%</td>
<td>P=0.004</td>
</tr>
</tbody>
</table>

AFP Appears to Be of Benefit for Early HCC Detection

Sensitivity of US with vs without AFP for early-stage HCC: 63% vs. 45% (p=.002)

Several Other Biomarkers Are Currently Undergoing Phase II-III Biomarker Evaluation

- AFP-L3 and DCP
- Golgi protein 73 (GP73)
- Glypican 3 (GPC3)
- Osteopontin
- miR-21 (circulating miRNA)
- Serum and urinary metabolites
- Fucosylated kininogen (Fc-Kin)
- Circulating tumor cells/methylated DNA markers
GALAD Is a Promising Novel Biomarker Panel for Early Detection

- **GALAD**: Gender, Age, AFP-L3, AFP, and DCP
- Multi-national nested case control with 6834 patients (2430 HCC, 4404 CLD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Correctly classified</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK cohort (all)</td>
<td>91.6%</td>
<td>89.7%</td>
<td>90.6%</td>
</tr>
<tr>
<td>UK cohort (Milan)</td>
<td>80.2%</td>
<td>89.7%</td>
<td>87.9%</td>
</tr>
<tr>
<td>Japan cohort (all)</td>
<td>70.5%</td>
<td>95.8%</td>
<td>87.2%</td>
</tr>
<tr>
<td>Japan cohort (Milan)</td>
<td>60.6%</td>
<td>95.8%</td>
<td>87.7%</td>
</tr>
<tr>
<td>Germany cohort (all)</td>
<td>87.6%</td>
<td>88.6%</td>
<td>88.3%</td>
</tr>
<tr>
<td>Germany cohort (unifocal &lt;5cm)</td>
<td>67.4%</td>
<td>88.6%</td>
<td>87.5%</td>
</tr>
</tbody>
</table>

No difference in GALAD performance by cirrhosis etiology, SVR, or HBV treatment

Potential Interventions to Improving Surveillance Effectiveness and Reducing HCC Moratility

**Increasing surveillance rates**
- Promoting education
  - Patient education
  - Practitioner training
  - Enlisting of primary care providers

**Improving compliance**
- Systems-level interventions
- Dedicated clinical pathways
- Clinical reminder systems
- Navigation programmes
- Mailed outreach

**Refinement of screening strategies**
- Risk stratification
- Predictive biomarkers
- Machine learning
- Low HCC risk
- Moderate/High HCC risk

**Recommended semi-annual ultrasound surveillance**

Screening using contrast-enhanced imaging

Early diagnosis biomarkers

HCC Surveillance Is Underused in Clinical Practice

Identified 29 studies between Jan 2010 – Aug 2018

Pooled surveillance estimate was only 26.1%

- Lower surveillance in US studies vs. Europe and Asia (17.8% vs. 43.2% and 34.6%)
- Higher surveillance in GI/Hepatology clinics vs. academic primary care clinics and population-based cohorts (73.7% vs. 29.5% and 8.8%)

Consistent correlates included higher surveillance with GI/Hepatology subspecialty care and increased number of clinic visits and lower surveillance in patients with NASH or alcohol-related cirrhosis.

Providers Report Potential Barriers to HCC Surveillance

<table>
<thead>
<tr>
<th>Provider-reported barriers</th>
<th>Safety-net health system (n=77)</th>
<th>Tertiary care system (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of knowledge about guidelines</td>
<td>68.2%</td>
<td>79.1%</td>
</tr>
<tr>
<td>Competing interests in clinic</td>
<td>51.6%</td>
<td>37.4%</td>
</tr>
<tr>
<td>Lack of time in clinic</td>
<td>40.5%</td>
<td>52.8%</td>
</tr>
<tr>
<td>Difficulty recognizing at-risk patients</td>
<td>35.4%</td>
<td>30.0%</td>
</tr>
<tr>
<td>Ultrasound capacity</td>
<td>23.0%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Responsibility of subspecialists &gt;PCP</td>
<td>5.3%</td>
<td>29.4%</td>
</tr>
</tbody>
</table>

Patients Report Barriers to HCC Surveillance

Presence of barriers independently associated with reduced HCC surveillance (aOR 0.62, 95% CI 0.41 – 0.94)

In-Reach and Outreach Interventions Can Significantly Increase HCC Surveillance

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Setting</th>
<th>Study Period</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Pre-Intervention [n (%)]</th>
<th>Post-Intervention [n (%)]</th>
<th>Absolute Difference</th>
<th>Relative Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberra, 2013</td>
<td>U. Michigan, USA</td>
<td>2008-2011</td>
<td>Nurse base protocol</td>
<td>One-time abdominal imaging</td>
<td>119/160 (74.4)</td>
<td>331/355 (93.2)</td>
<td>18.8%</td>
<td>25.3%</td>
</tr>
<tr>
<td>Kennedy, 2013</td>
<td>Flinders Medical Center, Australia</td>
<td>2007-2009</td>
<td>PCP and patient education system redesign</td>
<td>Semi-annual US and AFP for two years</td>
<td>0/22 (0)</td>
<td>14/22 (63.6)</td>
<td>63.6%</td>
<td>-</td>
</tr>
<tr>
<td>Beste, 2015</td>
<td>Northwest Veterans Affairs, USA</td>
<td>2011-2012</td>
<td>EMR Reminder</td>
<td>≥2 abdominal imaging within 18 months</td>
<td>103/564 (18.2)</td>
<td>218/790 (27.6)</td>
<td>9.4%</td>
<td>51.6%</td>
</tr>
<tr>
<td>Del Poggio, 2015</td>
<td>120 PCPs, Italy</td>
<td>1994-2013</td>
<td>PCP Education</td>
<td>HCC diagnosed by surveillance</td>
<td>85/244 (34.8)</td>
<td>105/190 (55.3)</td>
<td>20.5%</td>
<td>58.9%</td>
</tr>
<tr>
<td>Nazareth, 2016</td>
<td>Royal Perth Hospital, Australia</td>
<td>2010-2015</td>
<td>Nurse-led clinic</td>
<td>Semi-annual ultrasound</td>
<td>-</td>
<td>40/76 (52.6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Farrell, 2017</td>
<td>Royal Liverpool Hospital, UK</td>
<td>2009-2013</td>
<td>Radiology led recall</td>
<td>Semi-annual US</td>
<td>-</td>
<td>368/804 (45.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bui, 2017</td>
<td>KP Northern California, USA</td>
<td>Not reported</td>
<td>EMR identification and physician extender</td>
<td>3 abdominal imaging in 2 years</td>
<td>51/224 (22.8)</td>
<td>183/224 (81.7)</td>
<td>58.9%</td>
<td>258.3%</td>
</tr>
<tr>
<td>Signal, 2019</td>
<td>Parkland, Dallas, TX</td>
<td>2014-2016</td>
<td>Mailed outreach</td>
<td>Semi-annual US over 18 months</td>
<td>44/600 (7.3)</td>
<td>247/1200 (20.6)</td>
<td>13.3%</td>
<td>182.2%</td>
</tr>
</tbody>
</table>

Summary

• HCC surveillance supported by RCT in patients with chronic HBV and several cohort studies in those with cirrhosis

• Test accuracy and surveillance utilization are key factors for effectiveness

• Ultrasound has suboptimal sensitivity, particularly in contemporary cohorts
  – Novel blood- and imaging-based modalities are being evaluated

• Surveillance is underused in clinical practice due to patient- and provider-barriers
  – Intervention strategies show promise to increase utilization
Thank you!