Hepatocellular Carcinoma
Screening and Surveillance Strategies

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Fatima Medical Center
Is Surveillance “Worthwhile”? 

• How can we determine whether surveillance is worthwhile (effective)?

• How do we define “worthwhile”?
  – Improvement in survival of 3 months\(^1\)

• Surveillance considered cost-effective if it achieves this >3-month improvement in survival at a cost of < $50,000 per life-year saved\(^2\)

• Early diagnosis allows application of potentially curative treatment

• Detect 70% of tumors at early stage asymptomatic when it is possible to intervene.

Identification of At-Risk Population for HCC Surveillance

• What level of risk makes surveillance worthwhile?
  – Incidence

• According to randomized controlled trials
  – Hepatitis B: 0.28% per year\textsuperscript{[1]}

• According to cost-efficacy analyses
  – Hepatitis B: 0.2% per year\textsuperscript{[3]}
  – Non-hepatitis B cirrhosis: > 1.4% per year\textsuperscript{[4]}

HCC: Epidemiology

- HCC is the most common primary liver malignancy
- Worldwide incidence >600,000 new cases per year; (rising)
- More common in men than women (4:1)
- 80% occurs in developing countries particularly Asia
- In HBV endemic areas: >10 in 100,000
- 500,000 deaths worldwide per year

- For resection, rate of recurrence can be as high as 50% at 2 years
  - Only 12% are eligible for resection or LT
  - 80-90% of HCC cases occur in cirrhotic livers

Multifactorial Pathogenesis of HCC

Persistent/chronic hepatitis

Hepatitis → Cirrhosis → HCC

Cell death → Regeneration

Increasing Risk

- HBV
- HCV
- Alcohol
- Metabolic disorders
  - NASH
  - Hemochromatosis

HBV = hepatitis B virus; HCV = hepatitis C virus; NASH = nonalcoholic steatohepatitis.

### Risk Factors for Hepatocellular Carcinoma

#### Estimates of the Attributable Fractions (%)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Europe/US</th>
<th>Japan</th>
<th>Africa/Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatitis B virus</strong></td>
<td>22 (4-58)</td>
<td>20 (18-44)</td>
<td>60 (40-90)</td>
</tr>
<tr>
<td><strong>Hepatitis C virus</strong></td>
<td>60 (12-72)</td>
<td>63 (48-94)</td>
<td>20 (9-56)</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>45 (8-57)</td>
<td>20 (15-33)</td>
<td>- (11-41)</td>
</tr>
<tr>
<td><strong>Tobacco</strong></td>
<td>12 (0-14)</td>
<td>40 (9-51)</td>
<td>22 -</td>
</tr>
<tr>
<td><strong>Aflatoxin</strong></td>
<td>Limited</td>
<td>Limited</td>
<td>High exposure</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>&lt;5</td>
<td>-</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Bosch and Ribes Viruses and Liver Cancer, 2002

Ferlay et al. Int J Cancer 2010;127:2893-2917;
1. The tumor develops in the context of well-known environmental risk factors. The dominant role of HBV and HCV.

2. The tumor is strictly associated with chronic liver disease, mainly cirrhosis.

3. One of the few cancers not requiring histology for diagnosis in all cases. Radiological diagnosis possible in cirrhotics and HBV patients.

4. The sole solid cancer treatable by organ transplantation.
# Surveillance for HCC as Recommended by AASLD, APASL and EASL

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>AASLD 2010</th>
<th>APASL 2010</th>
<th>EASL 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target population</td>
<td>Cirrhosis, CHB&lt;sup&gt;1&lt;/sup&gt;, NAFLD</td>
<td>Viral Cirrhosis</td>
<td>Cirrhosis, CHB&lt;sup&gt;2&lt;/sup&gt;, HCV F3</td>
</tr>
</tbody>
</table>

<sup>1</sup> Asian males >40 years and females >50 years
Family history of HCC
African/North American blacks > 20 years

<sup>2</sup> Active hepatitis
Family history of HCC
Outcome of HCC Surveillance

- 18,816 people with HBV infection or history of chronic hepatitis in urban Shanghai, China enrolled
  - Surveillance group offered US and AFP every 6 months (n = 9373)
  - Control group received no surveillance (n = 9443)

<table>
<thead>
<tr>
<th></th>
<th>Total Incidence (per 100,000)</th>
<th>Rate ratio:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>223.7</td>
<td>1.37 (95% CI; 0.99-1.89)</td>
</tr>
<tr>
<td>Control</td>
<td>163.1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Total Mortality (per 100,000)</th>
<th>Rate ratio:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>83.2</td>
<td>0.63 (95% CI; 0.41-0.98)</td>
</tr>
<tr>
<td>Control</td>
<td>131.5</td>
<td></td>
</tr>
</tbody>
</table>

HBV: A Significant Cause of Worldwide Morbidity and Mortality

- > 2 billion have been infected\(^1\)
- 4 million acute cases per year\(^1\)
- 1 million deaths per year\(^1\)
- 350-400 million chronic carriers\(^1\)
  - 25% of carriers die from chronic hepatitis, cirrhosis, or liver cancer\(^1\)
  - Nearly 75% of chronic carriers are Asian\(^2\)
- Second most important carcinogen behind tobacco\(^3\)
- Causes 60% to 80% of all primary liver cancer\(^1\)
- HBV is 100 times more contagious than HIV\(^4\)
Hepatitis B Carriers Suitable for HCC Surveillance

Hepatitis B carriers\cite{1-4}

- Asian males $>\sim 40$ years (incidence $\sim 0.4\%$ to $0.6\%$ per year)
- Asian females $>\sim 50$ years (incidence $\sim 0.2\%$ per year)
- Africans older than 20 years of age (incidence unknown but likely $>0.2\%$ per year)
- Cirrhosis (HCC incidence: 3\% to 5\%/year)
- Family history of HCC: mainly Asian and African

## Surveillance for HCC as Recommended by AASLD, APASL and EASL/EORTC

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<td>Abdominal US +AFP</td>
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</tr>
<tr>
<td><strong>Optional CT/MRI</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Additional markers</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Screening intervals, mo.</strong></td>
<td>6</td>
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<td>CT, MRI &gt; 1 cm</td>
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# Sensitivity/specificity of AFP Surveillance for HCC

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-control studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trevisani 2001</td>
<td>60</td>
<td>91</td>
<td>25</td>
</tr>
<tr>
<td><strong>Surveillance studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanaka 1990</td>
<td>64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pateron 1994</td>
<td>50</td>
<td>86</td>
<td>33</td>
</tr>
<tr>
<td>Borzio 1995</td>
<td>47</td>
<td></td>
<td></td>
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<td>Sherman 1995</td>
<td>64</td>
<td>91</td>
<td>9</td>
</tr>
<tr>
<td>Solmi 1996</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoli 1996</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McMahon 2000</td>
<td>97</td>
<td>95</td>
<td>31</td>
</tr>
<tr>
<td>Bolondi 2001</td>
<td>41</td>
<td>82</td>
<td>46</td>
</tr>
<tr>
<td>Tong 2001</td>
<td>59</td>
<td>91</td>
<td>11</td>
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Serum AFP as a single test for the diagnosis of HCC has performed poorly and is not recommended as a surveillance test in management guidelines (41%-97% sensitivity)

*5% prevalence of HCC.

The Diagnostic Sensitivity of Ultrasound in the Early Diagnosis of HCC in Cirrhosis

Ultrasound alone

Ultrasound + AFP

Singal et al Aliment Pharmacol Ther 2009; 30:37-47
Combination of AFP and Ultrasound for Surveillance

• Combination increases detection, but increases false-positives and costs

• False-positive rates
  – AFP alone: 5.0%
  – Ultrasound alone: 2.9%
  – AFP/ultrasound combined: 7.5%

• Ultrasound costs $2000 per tumor found

• AFP/ultrasound costs $3000 per tumor found

Surveillance for HCC as Recommended by AASLD, APASL and EASL/EORTC

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HCC Surveillance by CT Scan

- No evidence to support the use of CT scanning for routine HCC surveillance
  - PPV and NPV unknown
  - Accurate use of CT requires 4-phase contrast CT
    - Radiation exposure is significant
  - In the absence of contrast CT, false-positive rate very high
    - Cannot distinguish small HCC from dysplastic nodules or arterialized cirrhotic nodules
    - Flow abnormalities create diagnostic difficulty
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Current Surveillance Tests Are Not Sufficiently Sensitive

- Prospective analysis of 99 patients with histologically proven, unresectable HCC

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Selecting an HCC Surveillance Interval

• Dependent on
  – Tumor growth rate
  – Prognosis of HCC at different sizes
    • < 1-2 cm
    • 2-3 cm
    • > 3 cm
  – Ideal surveillance interval unknown
    • Tumor growth rates suggest every 4-12 months

• Does not depend on degree of risk
HCC Surveillance Interval

- **Rationale for 6 month**
  - Doubling time: median = 6 mo (range, 1-19 mo)
  - Growth from 1 to 3 cm:
    - 4 mo for most aggressive,
    - 18 mo for moderately aggressive,
    - 5 yr for indolent

- **Median detectable subclinical period for HCC = 3.2%**
US Surveillance of HCC in Cirrhosis: Randomized Trial Comparing 3- and 6- Month Periodicity

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</table>
Radiological Diagnosis of 1-2 cm Nodules in Cirrhosis: A Surveillance study of 59 patients

<table>
<thead>
<tr>
<th>Imaging Method</th>
<th>No HCC</th>
<th>Sensitivity</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE-US</td>
<td>34</td>
<td>26%</td>
<td>100%</td>
</tr>
<tr>
<td>Contrast CT</td>
<td>34</td>
<td>44%</td>
<td>100%</td>
</tr>
<tr>
<td>MR gadolinium</td>
<td>32</td>
<td>44%</td>
<td>100%</td>
</tr>
<tr>
<td>Two coincidental technique of</td>
<td>35%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>stepwise imaging diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AASLD 2005)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential study with one</td>
<td>65%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>imaging</td>
<td></td>
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</tr>
</tbody>
</table>

A single technique of stepwise imaging diagnosis of HCC led to a 23% reduction of FNB procedures (p=0.031)

Sangiovanni A GUT 2010:59:638-44
Cumulative Survival Rates of HCC in Japan
The XVIII report of LCSG

Ikai, Hepatology Research 2010
Effect of Surveillance on Outcomes

• Retrospective analysis of patients with cirrhosis and HCC (N = 269)
  – Standard-of-care surveillance (n = 172)
    • Ultrasound or other abdominal imaging ≥ 1 time/year
  – Substandard surveillance (n = 48)
    • Lack of abdominal imaging within 1 year of cancer diagnosis
  – Absence of surveillance (n = 59)

<table>
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<tr>
<th>Outcomes, %</th>
<th>Standard-of-Care Surveillance (n = 172)</th>
<th>Substandard Surveillance (n = 48)</th>
<th>Absence of Surveillance (n = 59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC diagnosis at stages 1/2</td>
<td>69</td>
<td>35</td>
<td>18</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>32</td>
<td>13</td>
<td>7</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Mean 3-year survival from cancer diagnosis</td>
<td>40</td>
<td>27</td>
<td>13</td>
<td>&lt; .005</td>
</tr>
</tbody>
</table>

**NEVER ENDING: COST UTILITY RATIO**

Use of Surveillance for HCC among patients with cirrhosis in US

<table>
<thead>
<tr>
<th>Study</th>
<th>1873 cirrhotics + HCC 1994-2002, SEER Medicare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>17% regular 54% US</td>
</tr>
<tr>
<td>uptake</td>
<td>38% inconsistent 45% none</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elected for screening</th>
<th>Elected Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 182 (89%)</td>
<td>N=23(11%)</td>
</tr>
</tbody>
</table>

RUSH to JUDGEMENT?

Standard of Care and Not a Clinical Option

Davila, Hepatology 2010, Poustchi Hepatology 2011
Summary

• At-risk patients should be screened for HCC
• Ultrasound surveillance is preferable
  – AFP adds cost without significant benefit
• Serologic screening is not highly efficient
  – High false-positive and false-negative rates
• Surveillance should take place at 6-month intervals
  – Evidence for better survival than 12-month intervals
Screening and Surveillance are considered standard of care.
Cirrhosis (Non-HBV) Suitable for HCC Surveillance*

• Hepatitis C
  - Incidence of HCC ~ 2% to 8% per year
• Primary biliary cirrhosis
• Alcoholic cirrhosis
• Genetic hemochromatosis
• ? Nonalcoholic steatohepatitis
• ? Alpha1-antitrypsin deficiency
• ? Autoimmune hepatitis
• ? Cryptogenic cirrhosis


*Populations with an annual HCC incidence of ≥ 1.5%.
Sensitivity/Specificity of DCP and AFP as a Function of Disease Stage

- Effect of tumor size on the diagnosis of HCC by DCP, AFP