Liver Cancer Webinar
Epidemiology and Surveillance

Mario Strazzabosco, MD, PhD
Tamar H. Taddei, MD
Objectives

• Describe the incidence, prevalence, and impact of HCC in the United States
• Identify risk factors for HCC
• Recognize the importance of surveillance for HCC
• Identify who should undergo surveillance
• Describe how at-risk patients should undergo surveillance
HCC: An Epidemic…

- Hepatocellular carcinoma is rising in incidence globally, and tripled in the US in over the last three decades
- HCC is the leading cause of death in cirrhosis
- 5th most common cancer in men worldwide, 2nd leading cause of cancer death (>750,000 deaths/year)

Trends in incidence of liver cancer in selected countries: age-standardized rate per 100,000
5-Year Survival: Dismal

Figure 2. Age-Adjusted Incidence and 5-Year Survival Rates for Patients with Hepatocellular Carcinoma in the United States, 1973–2007.
HCC is Unique

• 1 patient, 2 diseases
  • Cirrhosis leads to
    • multifocal liver cancer
    • high recurrence rates
  • Cirrhosis complicates treatment and trial design
• Can be diagnosed by imaging alone
• The only solid organ malignancy for which transplantation offers a cure
The “Birth Cohort”

- Born before 1945 (aged > 55 years at death)
- Born 1945-1965 (aged 35-68 years at death)
- Born 1966-1970 (aged 35-47 years at death)
More than 75 percent of American adults with hepatitis C are baby boomers.

CDC recommends you get a blood test for hepatitis C if you were born 1945-1965.
Proper Identification and Surveillance is a Task for the Hepatologist!

Identifying high risk groups

Liver disease diagnosis

Cirrhosis diagnosis

Suspicious lesion

HCC Diagnosis

HCC Treatment

Recurrence of HCC

End of Life care

PRIMARY PREVENTION

Primary care and GI/Liver Subspecialty

SURVEILLANCE

Liver cancer Multidisciplinary Tumor Boards

SECONDARY PREVENTION

Cancer navigation Patient and provider support

- Control Metabolic Syndrome
- Eradication HCV
- Control HBV
- ETOH cessation, rehabilitation

- Evaluate Barriers
- Improve Access
- Patient navigation
- Risk stratification
5-Year Survival Is Substantially Higher When Liver Cancer Is Caught Early...

Percent of Cases by Stage

- Localized (43%)
- Regional (27%)
- Distant (18%)
- Unknown (13%)

5-year Relative Survival

- Localized: 31.1%
- Regional: 10.7%
- Distant: 2.8%
- Unstaged: 6.4%

National Cancer Institute.
Overview

• Describe the incidence, prevalence, and impact of HCC in the United States

• **Identify risk factors for HCC**

• Recognize the importance of surveillance for HCC

• Identify **who** should undergo surveillance

• Describe how at-risk patients should undergo surveillance
Insults Contributing to HCC

Hepatitis C
Hepatitis B
Aflatoxin
Alcohol
Autoimmune factors
Inherited factors
NASH
Cirrhosis
HCC

Viral Hepatitis is the Leading Risk Factor for HCC

### HCC Incidence by Etiology: Overall In the US

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>15-17%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>47-55%</td>
</tr>
<tr>
<td>Hepatitis C + alcohol</td>
<td>27% of above</td>
</tr>
<tr>
<td>Alcohol</td>
<td>9%</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
</tr>
<tr>
<td>No cirrhosis or virus</td>
<td>4%</td>
</tr>
</tbody>
</table>

### HCC Incidence by Etiology: US Urban Setting

- HBV: 60%
- HCV: 25%
- HBV + HCV: 3%
- Neither: 12%

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Achievement of a Sustained Virologic Response (SVR) in HCV Patients Does Not Mean that Risk for HCC is Eliminated

Incidence of HCC by SVR Status

Incidence of HCC:
HCV with and without SVR vs. Overall US Population

<table>
<thead>
<tr>
<th></th>
<th>Rate/100,000 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV w/o SVR</td>
<td>562</td>
</tr>
<tr>
<td>HCV w/SVR</td>
<td>410</td>
</tr>
<tr>
<td>Overall US Population</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Alcohol and Risk for HCC

*Standard drink = One 12-oz can of beer, one 5-oz glass of wine, one 1.5-oz shot of distilled 80-proof spirits.


Accessed February 8, 2015.
NASH and Risk for HCC

- NASH is the most severe form of NAFLD and is a frequent cause of cirrhosis.
- Common component of the metabolic syndrome.
- Prevalence estimated at 5.7% to 17% in the US.
- Epidemiologic data support association between NAFLD/NASH and HCC.
  - Primarily limited to patients with cirrhosis.
- Threshold at which surveillance should be started remains unknown.

NASH=nonalcoholic steatohepatitis; NAFLD=nonalcoholic fatty liver disease.

Obesity Increases Risk for Primary Liver Cancer and Death from Liver Cancer

- BMI ≥25 kg/m² associated with increased risk for primary liver cancer\(^1\)
- Liver cancer mortality rates 4.5-fold higher among men with a high BMI vs normal BMI\(^2\)

\(\text{Mortality from Liver Cancer by BMI}^2\)

\(\begin{array}{c|c|c|c|c}
\text{BMI (kg/m}^2) & 18.5-24.9 & 25.0-29.9 & 30.0-34.9 & 35.0-39.9 \\
\hline
9.24 & 10.49 & 19.22 & 47.8 \\
\end{array}\)

\(\text{BMI=body mass index.}\)

Prevalence of Obesity Over Time – 2014

Not Entirely to Blame...

United States Centers for Disease Control.
Impact of Diabetes on Risk for HCC

- Diabetes increases risk for HCC ~2.5-fold, probably through the development of NASH and cirrhosis\(^1\)
- HCC incidence doubled among patients with DM and increased with duration of disease\(^2\)

Data from 1985-1990.
DM=diabetes mellitus; NASH=nonalcoholic steatohepatitis.

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• Identify who should undergo surveillance
• Describe how at-risk patients should undergo surveillance
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><strong>AASLD</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>US +/- AFP every 6 months</td>
</tr>
<tr>
<td><em>American Association for the Study of Liver Diseases</em></td>
<td></td>
</tr>
<tr>
<td><strong>EASL</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>US every 6 months</td>
</tr>
<tr>
<td><em>European Association for the Study of the Liver</em></td>
<td></td>
</tr>
<tr>
<td><strong>APASL</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>AFP + US every 6 months</td>
</tr>
<tr>
<td><em>Asian-Pacific Association for the Study of the Liver</em></td>
<td></td>
</tr>
<tr>
<td><strong>NCCN</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>AFP + US every 6-12 months</td>
</tr>
<tr>
<td><em>National Comprehensive Cancer Network</em></td>
<td></td>
</tr>
<tr>
<td><strong>VA</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>AFP + US every 6-12 months</td>
</tr>
<tr>
<td><em>United States Department of Veterans Affairs</em></td>
<td></td>
</tr>
</tbody>
</table>
| **JSH-HCC**<sup>6</sup> | *High-Risk*: US every 6 months + AFP/DCP/AFP-L3 every 6 months  
*Very High-Risk*: US every 6 months + AFP/DCP/AFP-L3 every 6 months + CT/MRI (optional) every 6-12 months |
| *Japan Society of Hepatology* | |

AFP=alpha-fetoprotein; AFP-L3=*Lens culinaris* agglutinin-reactive fraction of AFP; CT=computerized tomography; DCP=des-γ-carboxyprothrombin; MRI=magnetic resonance imaging.

Outcomes Are Improved Among Patients who Undergo Routine HCC Surveillance

HCC Surveillance Is Associated with Early-stage Detection in Patients with Cirrhosis

2.08-fold improved odds of early detection

HCC Surveillance Is Associated with Improved Survival in Patients with Cirrhosis


1.90-fold improved odds of 3-year survival
## Evidence Favoring Surveillance

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N of participants (studies)</th>
<th>Overall quality of evidence</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early tumor detection rate</td>
<td>10,904 (38 observational studies)</td>
<td>☀☀ ☀☀ ⬤ □</td>
<td>OR 2.11 (1.88 to 2.33)</td>
</tr>
<tr>
<td>Early tumor detection rate (using BCLC to define early stage)</td>
<td>6,348 (23 observational studies)</td>
<td>☀☀ ☀☀ ⬤ □</td>
<td>OR 2.08 (1.80 to 2.37)</td>
</tr>
<tr>
<td>Early tumor detection rate (using BCLC to define early stage)</td>
<td>6,573 (6 observational studies)</td>
<td>☀☀ ☀☀ ⬤ □</td>
<td>OR 1.96 (1.41 to 2.73)</td>
</tr>
<tr>
<td>Curative treatment rate</td>
<td>24,374 (34 observational studies)</td>
<td>☀☀ ☀☀* ☬ ☧</td>
<td>OR 2.24 (1.99 to 2.52)</td>
</tr>
<tr>
<td>3-year survival rate*</td>
<td>10,850 (23 observational studies)</td>
<td>☀☀ ☀☀* ☬ ☧</td>
<td>OR 1.90 (1.67 to 2.17)</td>
</tr>
<tr>
<td>Early detection (ultrasound only)</td>
<td>(5 observational studies)</td>
<td>☀☀ ☀☀ ☬ ☧</td>
<td>OR 2.04 (1.55 to 2.68)</td>
</tr>
<tr>
<td>Early detection (ultrasound +/- AFP)</td>
<td>(14 observational studies)</td>
<td>☀☀ ☀☀ ☬ ☧</td>
<td>OR 2.16 (1.80 to 2.60)</td>
</tr>
<tr>
<td>Receipt of curative treatment (ultrasound only)</td>
<td>(8 observational studies)</td>
<td>☀☀ ☀☀ ☬ ☧</td>
<td>OR 2.23 (1.83 to 2.71)</td>
</tr>
<tr>
<td>Receipt of curative treatment (ultrasound +/- AFP)</td>
<td>(24 observational studies)</td>
<td>☀☀ ☀☀ ☬ ☧</td>
<td>OR 2.19 (1.89 to 2.53)</td>
</tr>
</tbody>
</table>

*Upgraded because of large effect size

Heimbach Hepatology 2017
Even Very High-risk Patients Rarely Receive Routine HCC Surveillance

Annual HCC Surveillance With Either US or AFP in Patients With HCV and Cirrhosis (n=9369)

Routine testing=tests done during at least 2 consecutive years in the 4 years after diagnosis of cirrhosis; inconsistent testing=≥1 test during the same timeframe.

AFP=alpha-fetoprotein; US=ultrasound.

Barriers to Surveillance

Underutilization

Provider

System/Patient

Test

Cirrhosis? Guidelines? Clinical concerns

Availability Scheduling Patient f/u

Operator-dependence
  • Tech v. MD
  • Obesity
## Primary Care Providers Report Multiple Barriers to HCC Surveillance

<table>
<thead>
<tr>
<th>Provider-reported barriers</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of knowledge about guidelines</td>
<td>68.2%</td>
</tr>
<tr>
<td>Competing interests in clinic</td>
<td>51.6%</td>
</tr>
<tr>
<td>Lack of time in clinic</td>
<td>41.5%</td>
</tr>
<tr>
<td>Difficulty recognizing at-risk patients</td>
<td>35.4%</td>
</tr>
<tr>
<td>Ultrasound capacity</td>
<td>23.0%</td>
</tr>
<tr>
<td>Doubt patients will complete</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

Overview

- Describe the incidence, prevalence, and impact of HCC in the United States
- Identify risk factors for HCC
- Recognize the importance of surveillance for HCC
- **Identify who should undergo surveillance**
- Describe how at-risk patients should undergo surveillance
### Who Is the High-risk Patient?

Groups in Whom the AASLD Recommends Routine Surveillance But in Whom Efficacy of Surveillance has Not Been Demonstrated

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Incidence of HCC/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhotic HBV carriers</td>
<td>3-8%</td>
</tr>
<tr>
<td>Hepatitis C cirrhosis</td>
<td>3-5%</td>
</tr>
<tr>
<td>Stage 4 primary biliary cholangitis with cirrhosis</td>
<td>3-5%</td>
</tr>
<tr>
<td>Asian male HBV carriers aged ≥40 years</td>
<td>0.4-0.6%</td>
</tr>
<tr>
<td>Asian female HBV carriers aged ≥50 years</td>
<td>0.3-0.6%</td>
</tr>
<tr>
<td>Hepatitis B carrier with family history of HCC</td>
<td>Higher than without family history</td>
</tr>
<tr>
<td>African/North African Blacks with HBV</td>
<td>HCC occurs at younger age</td>
</tr>
<tr>
<td>Genetic hemachromatosis and cirrhosis</td>
<td>Unknown (probably ~1.5%)</td>
</tr>
<tr>
<td>Alpha 1-antitrypsin deficiency and cirrhosis</td>
<td>Unknown (probably ~1.5%)</td>
</tr>
</tbody>
</table>

AASLD=American Association for the Study of Liver Disease; HBV=hepatitis B virus.

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• Describe the incidence, prevalence, and impact of HCC in the United States
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How Often Should Patients Undergo Surveillance?

- Observed survival:
  - 45 months with semiannual surveillance
  - 30 months with annual surveillance

- Single small (≤2 cm) tumors were 5-fold more frequent in semiannual surveillance group

Is More Frequent Than Semiannual Surveillance Beneficial?

<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>Final diagnosis of HCC within Milan criteria*</td>
<td>53 (30%)</td>
<td>70 (45%)</td>
</tr>
<tr>
<td></td>
<td>42 (79%)</td>
<td>50 (71%)</td>
</tr>
<tr>
<td>5-year survival</td>
<td>85%</td>
<td>86%</td>
</tr>
</tbody>
</table>

*Single tumor with diameter ≤5 cm or up to 3 tumors each with diameter ≤3 cm, no extrahepatic or major vessel involvement.

How to Conduct Surveillance?

Value of Ultrasound

- Surveillance ultrasound detects the majority of tumors of any stage
  - Sensitivity of 95%
- Less effective at detecting early HCC
  - Sensitivity of 63%

Predictors of Ultrasound Failure

• Retrospective study of 1170 patients evaluated causes of US failure:
  – HCC was found beyond Milan criteria in 32.2% of patients surveyed semiannually 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

AFP=alpha fetoprotein; BMI=body mass index; US=ultrasound.

The Role of AFP in Surveillance

AFP is inadequate as a marker for "diagnosis" of HCC in the absence of ultrasound and subsequent CT or MR imaging.
The Combination of AFP and US Is the Most Effective Strategy to Detect HCC at an Early Stage

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
<th>Sensitivity for early-stage HCCa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>21/41 (65.9)</td>
<td>363/401 (90.5)</td>
<td>7.0</td>
<td>0.38</td>
<td>19/41 (46.3)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>18/41 (43.9)b</td>
<td>367/401 (91.5)</td>
<td>5.2</td>
<td>0.61</td>
<td>13/41 (31.7)</td>
</tr>
<tr>
<td>Ultrasound and AFP</td>
<td>37/41 (90.2)b</td>
<td>334/401 (83.3)</td>
<td>5.4</td>
<td>0.12</td>
<td>26/41 (63.4)</td>
</tr>
</tbody>
</table>

AFP=alpha fetoprotein; US=ultrasound.

a Early-stage tumors were defined by the Milan criteria (one tumor <5 cm in maximum diameter or 3 tumors <3 cm each).

b When excluding the 10 patients without an ultrasound within 6 months of HCC diagnosis, sensitivity of ultrasound alone was 58.1% (18 of 31) and sensitivity of combination ultrasound/AFP was 87.1% (27 of 31).
CT Scanning for HCC Surveillance is Costly and Adds little Value

<table>
<thead>
<tr>
<th>Variable</th>
<th>US surveillance (n=83)</th>
<th>CT surveillance (n=80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC diagnosed</td>
<td>8 (10.8%)</td>
<td>8 (10.0%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Proportion of HCC at early stage (BCLC stage A)</td>
<td>5 (55.5%)</td>
<td>5 (62.5%)</td>
<td>0.93</td>
</tr>
<tr>
<td>False positive imaging</td>
<td>3 (3.6%)</td>
<td>9 (5.6%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cost per HCC detected</td>
<td>$17,041</td>
<td>$57,383</td>
<td></td>
</tr>
</tbody>
</table>

CT=computerized tomography; US=ultrasound.

Practical Considerations: Surveillance and Diagnosis

- 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.

*Blood tests AFP-L3/DCP

Gish RG. *Gastroenterol Hepatol (NY)*. 2014;10:121-123.
Take-home Points

• HCC is the most common presentation of primary liver cancer
• The incidence of liver cancer is increasing
• 5-year survival is dramatically higher among patients who are diagnosed with localized disease
• Less than half of patients are diagnosed with localized disease
• There are multiple risk factors that exponentially increase the risk.
Take-home Points

- Viral hepatitis is the number 1 risk factor for HCC
  - Patients who have achieved HCV SVR have a reduced risk for HCC
- Other risk factors include:
  - NASH
  - Obesity
  - Diabetes
  - Age
  - Male gender
  - Alcohol intake

HCV=hepatitis C virus; NASH=nonalcoholic steatohepatitis.
Take-home Points

• All major current guidelines recommend routine surveillance in at-risk patients
• Many patients are diagnosed at later stages of disease, when survival is poor
• Routine surveillance:
  – Improves early-stage detection
  – Increases the likelihood of curative treatment
  – Improves survival
• Despite the demonstrated value of routine surveillance, the vast majority of patients receive inconsistent or no surveillance
Take-home Points

- Data suggest that semiannual surveillance strikes a good balance among detection, cost, and patient convenience.
- US is the primary modality for routine surveillance.
- US has limited sensitivity, particularly in men, heavier patients, more advanced cirrhosis.
- AFP adds predictive value, particularly in settings where high-quality US may not be available and in patients at higher risk for screening failure.

AFP=alpha fetoprotein; US=ultrasound.