NEW YORK STATE
HCV PROVIDER CLASSIFICATION TRAINING
Hepatocellular Carcinoma Surveillance and Management

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Objectives

By the end of this presentation, learners should be able to

1. Describe risk factors for developing HCC
2. Describe surveillance for HCC in patients at risk.
3. Describe the impact of screening for HCC on survival.
4. Describe diagnostic modalities for HCC.
Surveillance for Hepatocellular Carcinoma (HCC)

- Screening
  - Application of diagnostic tests in patients at risk for HCC in whom no prior reason to suspect that HCC is present.

- Surveillance
  - The repeated application of screening tests.

Bruix J, Sherman M. *Hepatology*. July 2010. AASLD practice guidelines
Age-standardized incidence rates of hepatocellular carcinoma per 100,000 populations at risk, in different regions of world (Source: GLOBOCAN 2002).
Incidence Rate of Hepatocellular Carcinoma by Race in the US

Age-adjusted incidence rate of hepatocellular carcinoma by race based on SEER registry data from 1975-2007

- White: 1.2, 2.0, 3.7
- Black: 2.8, 4.0, 7.6
- Asian: 6.6, 8.4, 10.3
- Hispanic: 4.3, 8.2

Year:
- 1975-77
- 1993-95
- 2005-07
Age-Adjusted Incidence Rates of Liver Cancer in the US

Estimated Age-Standardized Rates per 100,000 Populations at Risk

Estimated age-standardized rates (World) per 100,000 populations at risk, in different regions of world (Source: GLOBOCAN 2012).
Emerging Trends in HCC: Incidence and Mortality

- Liver cancer is the 2\textsuperscript{nd} leading cause of cancer-related death in the world.
- HCC incidence and death rates are increasing in many parts of the world, including North America.
- In the US, HCC incidence rates increased by 3.1\% per year from 2008 to 2012
- In the US, death rates from HCC in men increased by 2.8\% per year and for women it increased by 3.4\% per year.

Risk Factors for Developing Hepatocellular Carcinoma

- Chronic Hepatitis/Cirrhosis
- NAFLD
- Hepatitis B
- Hepatitis C
- Alcoholics Liver Disease
- Aflatoxin
- Other Causes of Cirrhosis
## Surveillance for HCC

<table>
<thead>
<tr>
<th>Cirrhosis secondary to</th>
<th>Screening for Chronic hepatitis B carriers without cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis (B, C)</td>
<td>Asian man over age 40</td>
</tr>
<tr>
<td>Primary biliary cholangitis</td>
<td>Asian woman over age 50</td>
</tr>
<tr>
<td>Genetic hemochromatosis</td>
<td>African over age 20</td>
</tr>
<tr>
<td>A1-antitrypsin deficiency</td>
<td>Family history of HCC</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease</td>
<td>Any carrier older than age 40 with persistent or intermittent ALT abnormalities and/or HBV DNA &gt; 2000 IU/ml</td>
</tr>
<tr>
<td>Other cause of cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>

2010 AASLD Practice Guidelines

Impact of Screening on Survival After Diagnosis of HCC

<table>
<thead>
<tr>
<th></th>
<th>Screening Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>65.9</td>
<td>90.0</td>
</tr>
<tr>
<td>1-Year</td>
<td>59.9</td>
<td>31.2</td>
</tr>
<tr>
<td>2-Year</td>
<td>52.6</td>
<td>7.2</td>
</tr>
<tr>
<td>3-Year</td>
<td>52.6</td>
<td>7.2</td>
</tr>
<tr>
<td>4-Year</td>
<td>46.4</td>
<td>0.0</td>
</tr>
<tr>
<td>5-Year</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Impact of Screening on Stage of HCC at Time of Diagnosis

SVR to HCV Therapy Reduced HCC and Liver-Related Complications in Patients with Bridging Fibrosis or Cirrhosis

- Ascites, variceal bleeding.
- 307 HCV patients with bridging fibrosis (n=127) or cirrhosis (n=180) were evaluated by Cox regression analysis.
- Non-SVR in 67% of patients treated with pegylated interferon plus ribavirin. Median follow-up: 3.5 years.

# Risk Factors for HCC Development Among SVR Patients with Cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>SVR Patients with Cirrhosis</th>
<th>Median Follow-up (years)</th>
<th># Incident HCC</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Meer 2012</td>
<td>843 (84%)</td>
<td>6.7</td>
<td>50 (5%)</td>
<td>Age</td>
</tr>
<tr>
<td>Chang 2012</td>
<td>339 (38.9%)</td>
<td>3.5</td>
<td>37 (4.2%)</td>
<td>Age, F3-F4, AFP, thrombocytopenia</td>
</tr>
<tr>
<td>Arase 2013</td>
<td>149 (7.8%)</td>
<td>8.1</td>
<td>44 (2.3%)</td>
<td>Male, age, alcohol, diabetes</td>
</tr>
<tr>
<td>Huang 2014</td>
<td>86 (13.4%)</td>
<td>4.4</td>
<td>33 (5.1%)</td>
<td>Age, F4, GGT</td>
</tr>
</tbody>
</table>
Surveillance for HCC Post SVR

- SVR reduces HCC risk, but patients with fibrosis or cirrhosis remain at increased risk of HCC post SVR (annual incidence 0.5-2%).
- HCC risk persists for >10 years post SVR despite potential regression of fibrosis, surveillance may be needed indefinitely.
- HCC risk may plateau after first 6-7 years but unknown when falls below cost effectiveness threshold.
- Recurrence of HCC may increase post SVR.

Diagnosis of HCC

• Radiological diagnosis of HCC
• Role of AFP or serum markers
• Pathological diagnosis of dysplasia and early HCC
Ultrasound for HCC Surveillance

• Is not effective for surveillance of HCC in clinical practice (only 31.7% sensitive in early stage of HCC).

• Potential limitations of Ultrasound
  – Operator characteristics
  – Patient characteristics: obesity, liver echogenicity, ascites

• Improve effectiveness by better imaging quality, combining with biomarkers

## CT Scan for HCC Surveillance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ultrasound (N=83)</th>
<th>CT (n=80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of HCC</td>
<td>9 (10.8%)</td>
<td>8 (10.0%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Proportion BCLC A</td>
<td>5 (55.5%)</td>
<td>5 (62.5%)</td>
<td>0.93</td>
</tr>
<tr>
<td>HCC-related mortality</td>
<td>5 (6.0%)</td>
<td>7 (8.8%)</td>
<td>0.46</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</td>
<td>$17,041</td>
<td>$57,383</td>
<td></td>
</tr>
</tbody>
</table>

MRI for HCC Surveillance in Cirrhosis

- Prospective cohort study with 407 Child A-B patients
  - 1112 surveillances performed over 1.5 years
  - US and MRI in all patients
- 35 patients with total of 40 HCC nodules
- 26 patients had BCLC stage 0 and 8 patients BCLC stage A

<table>
<thead>
<tr>
<th>Cohort</th>
<th>MRI</th>
<th>US</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>97%</td>
<td>40%</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Sensitivity for BCLC 0</td>
<td>96%</td>
<td>42%</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Specificity</td>
<td>94%</td>
<td>90%</td>
<td>( P = 0.049 )</td>
</tr>
</tbody>
</table>

Lim Y. Nov 10, 2014. AASLD abstract 1338.
HCC Diagnosis Is Established by Imaging Criteria

- Intense contrast uptake in the arterial phase followed by contrast washout in the venous phase, and capsule is considered specific for HCC on MRI and CT.

- Nodules 1 cm or less may not be validated as tumor. Such nodules should be followed with serial studies.

- PET scans are not useful due to low sensitivity.
Non-Invasive Diagnosis: Arterial Enhancement, Venous Washout, Capsule and Threshold Growth
LIRADS System for HCC Diagnosis Schema

<table>
<thead>
<tr>
<th>Lesion Characteristics</th>
<th>Arterial Phase Hypo- or Iso-Enhancement</th>
<th>Arterial Phase Hyper-Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm):</td>
<td>&lt; 20</td>
<td>≥ 20</td>
</tr>
<tr>
<td></td>
<td>&lt; 10</td>
<td>10-19</td>
</tr>
<tr>
<td>• “Washout”</td>
<td>LR-3</td>
<td>LR-3</td>
</tr>
<tr>
<td>• “Capsule”</td>
<td>LR-3</td>
<td>LR-4</td>
</tr>
<tr>
<td>• Threshold growth</td>
<td>LR-4</td>
<td>LR-4</td>
</tr>
</tbody>
</table>


One: LR-4, LR-4, LR-4, LR-4, LR-5, LR-5

≥ Two: LR-4, LR-4, LR-4, LR-4, LR-5, LR-5
Liver Biopsy in the Diagnosis of HCC

- Biopsy of small nodule within a cirrhotic liver seen on imaging studies may not be reliable.
- Sampling error occurs.
- Distinguishing HCC from dysplastic nodule is often erroneous.
- A “negative” biopsy can not rule out malignancy.
- Up to 30% of HCC patients can have a “non diagnostic” biopsy or tumor is inaccessible.
## Diagnostic Values of HCC Biomarkers

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP-L3</td>
<td>61.6</td>
<td>92</td>
</tr>
<tr>
<td>DCP</td>
<td>72.7</td>
<td>90</td>
</tr>
<tr>
<td>AFP</td>
<td>67.7</td>
<td>71</td>
</tr>
<tr>
<td>AFP-L3 + DCP</td>
<td>84.8</td>
<td>97.8</td>
</tr>
<tr>
<td>AFP-L3 + AFP</td>
<td>73.7</td>
<td>86.8</td>
</tr>
<tr>
<td>DCP + AFP</td>
<td>84.8</td>
<td>90.2</td>
</tr>
</tbody>
</table>

DCP: des-gamma carboxy prothrombin  
*World J Hepatol.* 2015 Feb 27; 7 (2): 139-149.
HCC Surveillance

- Ultrasound with AFP improves sensitivity for tumor, and early tumor detection respectively in clinical practice.
- Ultrasound with AFP every 6 months appears to be the optimal surveillance strategy to maximize early HCC detection.
- MRI has higher sensitivity for detection of early tumor in patient with cirrhosis.

Diagnostic Algorithm for Hepatocellular Carcinoma (AASLD 2010 Practice Guidelines)

Liver nodule

< 1 cm
- Repeat US at 3 months
  - Growing/changing character → Investigate according to size
  - Stable

> 1 cm
- 4-phase MDCT/dynamic contrast enhanced MRI
  - Arterial hypervascularity AND venous or delayed phase washout
    - Other contrast enhanced study (CT or MRI)
      - Arterial hypervascularity AND venous or delayed phase washout
        - Yes → HCC
        - No
          - Biopsy
Barcelona Clinic Liver Cancer Staging System and Treatment Strategy for HCC

BCLC Staging and Treatment Schedule

Stage 0
PST 0, Child-Pugh A

- Very early stage (0)
  - Single <2cm, Carcinoma in situ
    - Portal pressure/bilirubin
      - Increased → Resection
      - Normal

Stage A
Okuda 1-2, PST 0-2, Child-Pugh A-B

- Early stage (A)
  - Single or 3 nodules ≤ 3cm, PS 0

Stage B
Multinodular, PS 0

Stage C
Portal invasion, N1, M1, PS 1-2

Stage D
Okuda 3, PST >2, Child-Pugh C

Terminal stage (D)

Curative Treatments (30%)
5-yr survival: 50-70%

Liver Transplantation (CLT/LDLT)
Resection

PEI/RF
3 nodules ≤3cm

Associated diseases
No → PEI/RF
Yes

Intermediate stage (B)
Multinodular, PS 0

Chemoembolization

Randomized controlled trials (50%)
3-yr survival: 20-40%

New Agents

Symptomatic (20%)
1-yr survival: 10-20%

Increased
No
Yes

Associated diseases

Increased

Management Strategies for HCC

• Prevention:
  – Promote hepatitis B vaccination.
  – Treat chronic hepatitis B, C and other chronic liver disease.
  – Reduce the development of cirrhosis and progression to HCC.

• Early diagnosis
  – Surveillance for hepatocellular carcinoma in patients at risk by optimal screening tests.
HCC Treatment: A Multidisciplinary Approach

• By hepatologists, transplant and hepatobiliary surgeons, medical oncologists, interventional radiologists, and palliative care specialists.

• Curative therapy for HCC
  – Liver transplantation is the most effective treatment
  – Surgical resection for resectable disease in the absence of significant portal hypertension
  – Local ablation is as effective as surgical resection in very early or early stage
HCC Treatment: A Multidisciplinary Approach

• Trans-arterial chemo or radio-embolization
  – to downstage patients at intermediate/advanced stage
  – to prevent tumor progression while on the wait-list for OLT

• Sorafenib achieves modest prolongation of survival of patient with advanced stage HCC

• Future perspectives to improve clinical outcome of HCC
  – Immunotherapy
  – Targeted therapy
Summary

• Prevent HCC by hepatitis B immunization, and treatment of chronic liver diseases.

• Reduce the development of cirrhosis and progression to HCC.

• Diagnose early HCC in patients at risk by surveillance.

• Abdominal US with AFP every 6 months appears to be the optimal surveillance strategy to maximize early HCC detection.

• MRI has higher sensitivity for detection of early tumor in patient with cirrhosis.

• Improve the outcome of HCC by appropriate treatment through multidisciplinary approach.