Updates in Hepatocellular Carcinoma

Kimberly Brown, MD, FAASLD, FAST, AGAF
Professor of Medicine Wayne State University
Chief Division of Gastroenterology and Hepatology
Associate Medical Director Henry Ford Hospital Transplant Institute
Henry Ford Hospital, Detroit
The Global Impact of Liver Cancer

- Liver cancer
  - 6th most common cancer
  - 2nd most frequent cause of cancer-related death globally
    - 854,000 new cases and 810,000 deaths per year

- HCC (hepatocellular carcinoma)
  - Accounts for 80-90% of primary liver cancers
  - Constitutes a major global health problem
Incidence in the U.S.

Malignant Transformation

- Normal liver
- Hepatitis C
- Hepatitis B
- Ethanol
- NASH
- Liver cirrhosis
- Dysplastic nodules\(^1\)
- Epigenetic alterations
- Genetic alterations
- HCC\(^2\)


These slides are the property of the presenter. Do not duplicate without permission.
Incidence of HCC is rising

Top 15 causes of cancer death
United States 2010-2014

- Lung: -2.5%
- Colon & rectum: -2.5%
- Breast: -1.9%
- Pancreas: +0.1%
- Prostate: -0.9%
- Leukemia: +0.4%
- Liver (#7): +2.7%
- Lymphoma: -2.6%
- Bladder: -2.3%
- Brain: -1.1%
- Esophagus: -2.5%
- Ovary: -0.8%
- Kidney: -0.6%
- Myeloma: -2.3%
- Stomach: -2.3%

Annual Percent Change (2000 – 2014)

www.seer.cancer.gov
HCC Mortality from 1990-2015...

High Mortality Rates in HCC

518 untreated patients: survival stratified by stage

HCC Risk Factors

- Worldwide – chronic viral hepatitis
  - HBV accounts for >50% cases worldwide
  - US and Europe – HCV is greatest risk factor
- Cirrhosis, all etiologies
  - Annual risk of 2-7%
  - Lifetime risk of 33% (overall)
- Advancing age, male gender (2.4:1), obesity, diabetes, HIV co-infection, *Aflatoxin* exposure, alcohol/tobacco


*These slides are the property of the presenter. Do not duplicate without permission.*
Alcohol and HCC risk


These slides are the property of the presenter. Do not duplicate without permission.
NAFLD and HCC risk


These slides are the property of the presenter. Do not duplicate without permission.
# HCC preventive interventions

<table>
<thead>
<tr>
<th>Liver disease progression</th>
<th>Chronic hepatitis</th>
<th>Advanced fibrosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC progression</td>
<td>Normal hepatocyte</td>
<td>Subclinical molecular/</td>
<td>Diagnosed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>histological IEN</td>
<td>1st primary HCC</td>
</tr>
<tr>
<td>Type of prevention</td>
<td>Primary</td>
<td>Secondary</td>
<td>Tertiary (adjuvant)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HCC screening</td>
</tr>
<tr>
<td>Potential chemoprevention strategies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiviral therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-inflammation therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-fibrotic therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic disease treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular targeted therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

These slides are the property of the presenter. Do not duplicate without permission.
Modifying HCC risk

- Universal Hepatitis B vaccination
  - Primary prevention of HCC

- Antiviral treatment of chronic HBV

- Treatment of HCV to achieve SVR

- Decreased Aflatoxin exposure through public health efforts in developing countries
  - WHO and CDC working groups (2005-current)
Impact of Universal Vaccination in Taiwan

Chang MH. NEJM 1997

These slides are the property of the presenter. Do not duplicate without permission.
Hep B viral load and HCC incidence

REVEAL Study (n=3,653)

Baseline HBV DNA level, copies/mL

- ≥10^6 (n=627) 14.9%
- 10^5–<10^6 (n=349) 12.2%
- 10^4–<10^5 (n=643) 3.6%
- 300–<10^4 (n=1,161) 1.4%
- <300 (n=873) 1.3%

Cumulative incidence of HCC (% subjects)

Log rank test of trend
p<0.001

Year of follow-up

Chen CJ. JAMA 2006.

These slides are the property of the presenter. Do not duplicate without permission.
Antiviral Therapy in Hepatitis B

“Proof of Principle”

Lamivudine (n=436)
Placebo (n=215)

P=0.001

Patients with disease progression (%)

Time to disease progression (months)


These slides are the property of the presenter. Do not duplicate without permission.
HCV treatment reduces HCC risk

- SVR vs no SVR (0.90 vs 3.45 HCC/100 person-years; HR 0.28)
- Cirrhosis + SVR vs. no Cirrhosis + SVR (1.82 vs 0.34/100 person-years; HR 4.73)

Surveillance for HCC

- Recommended for high-risk populations

- RCT from China showing survival benefit
  - US + AFP every 6 months vs. no surveillance
  - Chronic HBV patients +/- cirrhosis

- No RCT in cirrhosis patients
  - Several prospective cohort studies
  - Surveillance → earlier stage of diagnosis and better survival

Surveillance improves early stage diagnosis


These slides are the property of the presenter. Do not duplicate without permission.
Surveillance for HCC Reduces Mortality
A Randomized Controlled Trial

HCC-related mortality reduced by 37%

Surveillance improves survival in cirrhosis


These slides are the property of the presenter. Do not duplicate without permission.
Surveillance for HCC

• AASLD:
  • Ultrasound every 6 months
    • Pooled sensitivity of 63% for early-stage (32% in clinical practice)
  • AFP with US increases sensitivity to 63.4% (clinical practice)
    • Optimal clinical strategy*
  • Other biomarkers
    • AFP (cutoff >10.9 ng/mL) more sensitive than AFP-L3 or DCP or Glypican 3 for early-stage HCC


These slides are the property of the presenter. Do not duplicate without permission.
Surveillance for HCC

Surveillance benefit

- Asian male hepatitis B carriers over age 40
- Asian female hepatitis B carriers over age 50
- Hepatitis B carrier with family history of HCC
- African and/or North American blacks with hepatitis B
- Hepatitis B carriers with cirrhosis
- Hepatitis C cirrhosis
- Stage 4 PBC
- Genetic hemochromatosis and cirrhosis
- Alpha-1 antitrypsin deficiency and cirrhosis
- Other cirrhosis

Surveillance benefit uncertain

- Hepatitis B carriers younger than 40 (males) or 50 (females)
- Hepatitis C and stage 3 fibrosis
- NAFLD without cirrhosis
Surveillance rates for HCC

Pooled meta-analysis: <20% surveillance rates for cirrhotic patients

Singal AG. J Gen Int Med 2012.
## PCP reported barriers to 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>


*These slides are the property of the presenter. Do not duplicate without permission.*
Diagnosing HCC

Key Points:

• Consider pre-test probability
  • w/o underlying liver disease - hemangioma, FNH, or metastasis most common

• High quality imaging is key
  • Multi-phasic CT or MRI

• Biopsy needed <10% of the time
  • Sampling error, bleeding, tumor seeding
Dual Blood Supply of Liver

- Vascular supply of HCC arises from the hepatic artery through neovascularization.

- Multi-phase imaging is key

- Radiological hallmark: arterial hypervascularity with washout in the venous/delayed phase

Yu JS. Am J Roentgenol 1999

These slides are the property of the presenter. Do not duplicate without permission.
HCC Diagnosis

Triple Phase Imaging of Hepatocellular Carcinoma

Pre-contrast  Arterial Phase  Portal Venous/ Delayed
Washout in HCC
HCC Staging

- Staging is used for prognosis and to guide treatment

- Factors affecting staging systems
  - Tumor stage
  - Liver function
  - Functional status

- Links stage with treatment options and prognosis

BCLC Staging System

- BCLC was best predictor of survival
- Homogeneity in survival across each stage
- Validated BCLC compared to other staging systems

Survival Probability

Time (Months)

Log Rank P
A vs. B  P < .0001
B vs. C  P = .04
C vs. D  P = .01
Barcelona Staging

HCC Staging & Prognosis

HCC

Stage 0
PST 0, Child-Pugh A
Very early stage (0)
Single <2 cm, Carcinoma in situ
Single
Portal pressure/bilirubin
Increased
Normal
Resection
Liver transplantation (CLT/LDLT)
Curative treatment (30-40%)
Median OS >60 mo; 5-yr survival: 40-70%

Stage A-C
PST 0-2, Child-Pugh A-B
Early stage (A)
Single or 3 nodules ≤3 cm, PS 0
3 nodules ≤3 cm

Intermediate stage (B)
Mеланодермод, PS 0

Advanced stage (C)
Portal invasion, N1, M1, PS 1-2

Stage D
PST >2, Child-Pugh C*
Terminal stage (D)

Associated diseases
No
Yes
RF/PEI
Target: 20%
OS: 20 mo (45-14)
TACE
Target: 40%
OS: 11 mo (6-14)
Sorafenib
Target: 10%
OS: <3 mo

Best supportive care

These slides are the property of the presenter. Do not duplicate without permission.
Treatment of Early Stage HCC

EASL CPG. J Hep 2018.

These slides are the property of the presenter. Do not duplicate without permission.
Outcome of Surgical Resection for HCC in Cirrhosis

Patients with a single tumor
 <= 5 cm and Child A cirrhosis

Months

Probability (%)

Portal pressure, Bili < 1
NL portal pressure, Bili < 1
Portal pressure, Bili ≥ 1

Log Rank 0.00001

0 12 24 36 48 60 72 84 96

*Other surrogates for portal htn = HVPG ≥ 10mmHg ; plt <100

Patients with a single tumor
 <= 5 cm and Child A cirrhosis

Liver Transplant for HCC

Four-Year Survival

Unselected 1991: 40%
Milan Criteria: 75%
Other Dx: 76%

Mazzafero V. NEJM 1996.

These slides are the property of the presenter. Do not duplicate without permission.
Intermediate HCC (Stage B)
Chemoembolization

Prolongs 2-yr survival: 63% vs. 27% for best supportive care (p<0.001)

Radioembolization with Yttrium (Y90) microspheres in HCC (TARE)

- Brachytherapy via hepatic artery

- Median survival:
  - 17 mo for intermed stage
  - 7-12 mo for advanced stage or PVT

TARE likely has a role for Intermediate Stage HCC

TTP: >26 vs. 6.8 months (HR 0.12, 95%CI 0.03-0.56)

Median survival: 17.7 vs. 18.6 mo (p=0.99)

SHARP: Overall Survival Sorafenib

Sorafenib median:
46.3 weeks (10.7 months)
(95% CI, 40.9-57.9)

Placebo median:
34.4 weeks (7.9 months)
(95% CI, 29.4-39.4)

Llovet JM et al. NEJM 2008.

These slides are the property of the presenter. Do not duplicate without permission.
SHARP results

• Doubling of TTP
  • Sorafenib 5.5 mo vs. Placebo 2.8 mo ($P<.001$; HR: 0.58; 95% CI, 0.45-0.74)

• Study stopped early due to efficacy

• Parallel study in Asian-Pacific population
  • Mostly hepatitis B patients
  • More advanced disease, ECOG 1-2 or metastatic disease

Llovet JM et al. NEJM 2008.
Subsequent negative HCC trials...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment</th>
<th>Patients</th>
<th>Trial results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>1074</td>
<td>7.9 vs. 10.2 months</td>
</tr>
<tr>
<td>Brivanib</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>1150</td>
<td>9.5 vs. 9.9 months</td>
</tr>
<tr>
<td>Linafinib</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>1035</td>
<td>9.1 vs. 9.8 months</td>
</tr>
<tr>
<td>Erlotinib/sorafenib</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>720</td>
<td>9.5 vs. 8.5 months</td>
</tr>
<tr>
<td>Brivanib</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>395</td>
<td>9.4 vs. 8.2 months</td>
</tr>
<tr>
<td>Everolimus</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>546</td>
<td>7.6 vs. 7.3 months</td>
</tr>
</tbody>
</table>
Lenvatinib is non-inferior to Sorafenib

Current treatment landscape...

- Advanced (BCLC C)
- Sorafenib or Lenvatinib
- Regorafenib or Nivolumab or Pembrolizumab or Cabozantinib or Ramucirumab*

* If AFP > 400 ng/mL
Henry Ford HCC: Multidisciplinary Approach

- Hepatology
- Hepatobiliary Surgery
- Pathology
- Radiation Oncology
- Oncology
- Radiology

These slides are the property of the presenter. Do not duplicate without permission.
Conclusion – Key Learnings

- Prevention of HCC is targeted to risk reduction through modification of risk factors and treatment of viral hepatitis
- HCC surveillance improves early diagnosis and survival in patients with cirrhosis
- Staging of HCC is dependent on tumor, liver and patient characteristics
- Current therapies for HCC are dependent on staging
- Options for HCC treatment are best discussed in a multi-disciplinary setting
- Rapid advancement in medical therapies along with studies evaluating combination treatments are anticipated to improve overall survival in this patient population