Hepatocellular Carcinoma: The growing disease burden

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Hepatocellular Carcinoma (HCC)

- Hepatocellular carcinoma (HCC) is the 6th most common cancer in the world

- Third leading cause of cancer related death

- Age-adjusted US incidence has increased 2-fold: 1985-1998

- American Cancer Society statistics for liver cancer in 2008
  - Most patients with HCC in US have liver cirrhosis mainly by hepatitis B and C viruses
  - Estimation of new cases: 21,370
  - Estimation of deaths: 17,000
HCC: Epidemiology

- Hepatitis B virus is the most frequent underlying cause worldwide.
- 85% of HCC cases occur in Eastern and Southeastern Asian and Sub Saharan Africa (endemic HBV infection).
- In the US, HCV-related HCC is a rapidly rising cancer (50-70% of cases).
- Other risk factors in the United States include alcohol use, nonalcoholic fatty liver disease, inherited liver disease, smoking:
  - Hemochromatosis (highest risk, though low disease penetrance).
- Cirrhosis is a pre-malignant condition.
Rising Mortality Rate from HCC in US (Age Adjusted)
Age-Specific Incidence of HCC among White Men in SEER Database
Origin of HCC

- Cirrhotic liver
  - All causes
- Noncirrhotic liver
  - Hepatitis B
  - Fibrolamellar variant
  - Rare metabolic diseases (eg, glycogenosis, porphyria)
  - Hepatitis C (rare)
  - Other
Incidence of HCC as it relates to etiology of cirrhosis

Cirrhosis: High incidence of HCC (>15%)
- Hemochromatosis
- HCV-related
- HBV-related
- Alcoholic cirrhosis with HCV

Cirrhosis: Intermediate incidence of HCC (5%-15%)
- Alcoholic cirrhosis without HCV
- Non-alcoholic fatty liver disease

Cirrhosis: Low incidence of HCC (<5%)
- Primary biliary cirrhosis
- Wilson disease cirrhosis
- Autoimmune hepatitis
REVEAL: Baseline HBV DNA and Liver Disease Progression

Prospective, multicenter, observational cohort study

1991-1992: 7 Taiwanese townships
Individuals aged 30-65 years eligible
(N = 89,293)

HCC-free individuals enrolled
(n = 23,820)

Excluded if cirrhotic within 6 months

Cirrhosis Analysis
(n = 3774)
2004: 42,115 PYs follow-up
395 cirrhotic patients (10.5%)

HCC Analysis
(n = 3653)
2004: 41,779 PYs follow-up
164 HCC patients (4.5%)

REVEAL Study: HBV DNA Levels and Long-Term Outcomes

Viral Load at Baseline

- < 300 (Undetectable)
- 300-9,999
- 10,000-99,999
- ≥ 1 Million

Cumulative incidence of HCC (%)(n = 3653)

- < 300 (Undetectable): 1.30%
- 300-9,999: 1.37%
- 10,000-99,999: 14.89%

Multivariate-adjusted relative risk of cirrhosis (n = 3482)

- < 300 (Undetectable): 1.0
- 300-9,999: 2.0
- 10,000-99,999: 3.6
- ≥ 1 Million: 9.7, 10.6


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HCC: Pathogenesis

• Carcinogenesis is typically a stepwise process
  – Sequential genetic mutations
  – Oncogene activation
  – Tumor suppressor gene inactivation

• No dominant pathways of hepatocellular carcinogenesis have been identified
Molecular Pathogenesis of HCC

- 2 key mechanisms implicated in development of HCC
  - Liver cirrhosis following tissue damage (infectious or toxic damage)
  - Mutations occurring in 1 or more oncogenic or tumor suppressor genes
- Abnormalities in cellular signaling pathways
  - Raf/MEK/ERK
  - PI3K/AKT/mTOR
  - Wnt/β-catenin
  - Angiogenic signaling

HCC
Possible Premalignant Lesions

- Dysplastic Nodules
- Large Cell Dysplasia
- Macroregenerative Nodules
- Small Cell Dysplasia

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Growth Rates of HCC

Median Doubling Time = 117 Days (Range: 29-398)

Actuarial Survival of Patients With Untreated HCC

Probability (%)

Patients at Risk


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Spread of HCC

Extrahepatic Spread to:
- Lungs
- Bone
- Adrenals
How do we screen for HCC

• No studies define unequivocally the best modality for diagnosing HCC

• Ultrasonography (US) every 6-12 months with alpha-fetoprotein (AFP) every six months is current standard of care for screening high risk patients
  • US has technical limitations (operator dependence, reduced efficacy in those with elevated BMI)
  • US if subject has normal BMI

• AFP alone is not sufficient unless imaging modalities are not available

• Our practice at IU: MRI every 9 months or Dual Phase Spiral CT, or US every 6-12 months if normal BMI
  • MRI or US preferred due to radiation risk with CT scan
AASLD Guidelines

• Surveillance recommended in at-risk groups
  – Specific hepatitis B carriers
  – Nonhepatitis B cirrhosis

• US preferred surveillance tool
  – AFP alone should not be used unless US unavailable

• Patients should be screened at 6- to 12-month intervals
HCC Screening: Caveats with Ultrasound

- Detection of hypo- or hyperechoic nodule should raise suspicion of HCC in a cirrhotic patient
  - Less than half of nodules less than 1 cm size correspond to hepatocellular carcinoma
  - Nodules less than 1 cm are followed with repeat ultrasound every three months until lesion greater than 1 cm
  - Absence of growth does not rule out HCC
How is HCC Diagnosed: Dynamic Imaging (CT scan or MRI)

- HCCs have blood supply from hepatic artery
- Dual Phase Spiral CT scan or MRI with intravenous contrast allows rapid acquisition of images during hepatic arterial phase and portal venous phases
- Lesions seen during the arterial phase and which are less well seen during portal venous phase are suspicious for HCC
  - Requires relatively preserved renal function for both
Figure 2. CT scan of the liver demonstrating an early HCC. This lesion is hypervascular, thus enhancing after contrast injection and appearing as a hyperdense nodule.
How is HCC Diagnosed: MRI

- MRI provides another way of distinguishing hepatocellular carcinoma from normal liver tissue.
- Most tumors have a low signal intensity on $T_1$-weighted images and a high signal intensity on $T_2$-weighted images.
- Gradient-echo sequences and turbo spin-echo sequences have greatly reduced the time needed for MRI.
  - (breath holding for 40 seconds for optimal images)
- Less dependent on normal renal function.

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MRI demonstrating HCC/Tumor Thrombosis
How is HCC Diagnosed?

• Nodules >2 cm can be confidently diagnosed with CT or MRI without needing a biopsy positive for HCC

• If lesion 1-2 cm need 2 dynamic imaging studies with typical washout, otherwise, biopsy

• A biopsy of a nodule negative for HCC should never be accepted as having excluded malignancy
Mass found with surveillance

Mass on surveillance ultrasound in a cirrhotic liver

- **< 1 cm**
  - Repeat US at 3-4 month intervals
  - Stable over 18-24 months
    - Return to standard surveillance protocol (6-12 monthly)
    - Proceed according to lesion size
  - Enlarging

- **1-2 cm**
  - Two dynamic imaging studies
    - Coincidental typical vascular pattern on dynamic imaging
      - Stable over 18-24 months
        - Repeat US at 3-4 month intervals
        - Proceed according to lesion size
      - Enlarging
        - Biopsy
          - Diagnostic of HCC
            - Repeat biopsy or imaging follow-up
              - Change in size/profile
                - Repeat imaging and/or biopsy
                  - Positive
                    - Treat as hepatocellular carcinoma
                  - Negative
          - Non diagnostic
          - Other diagnosis

- **> 2 cm**
  - One dynamic imaging technique
    - Atypical vascular pattern
      - Typical vascular pattern or AFP > 200 ng/mL
      - Typical vascular pattern on dynamic imaging or AFP > 200 ng/mL
        - Repeat biopsy or imaging follow-up
          - Change in size/profile
            - Repeat imaging and/or biopsy
              - Positive
                - Treat as hepatocellular carcinoma
              - Negative
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>
<thead>
<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>
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</tbody>
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Alpha-fetoprotein Levels

• Values greater than 400 ng/ml have been validated as confirming hepatocellular carcinoma.

• Viral liver disease often associated with transient increases of AFP coinciding with inflammatory flares of disease.

• Values > 200 ng/ml with mass associated with high likelihood of HCC.

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Staging of HCC

- Staging systems
  - TNM nomenclature
  - Okuda system
  - BCLC (Barcelona Clinic Liver Cancer)
  - CLIP (Cancer of the Liver Italian Program)

- Key features
  - Tumor size
  - Liver function
  - Performance status of the patient
HCC
Factors Affecting Survival

- Constitutional syndrome
- Performance status
- Vascular invasion
- Extrahepatic spread

Prognosis of Patients With HCC
Patient Survival

<table>
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<tr>
<th>Therapy</th>
<th>1 Year</th>
<th>3 Years</th>
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</thead>
<tbody>
<tr>
<td>No “radical” therapy</td>
<td>54%</td>
<td>28%</td>
</tr>
<tr>
<td>Surgical resection</td>
<td>81%</td>
<td>44%</td>
</tr>
<tr>
<td>Ethanol injection</td>
<td>82%</td>
<td>38%</td>
</tr>
<tr>
<td>Transplantation</td>
<td>84%</td>
<td>74%</td>
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HCC Treatment Options: 2008

- Surgical resection
- Liver transplantation
- Transarterial Chemo-embolization or Radioembolization (Yttrium-90 microspheres)
- Radiofrequency ablation
- Sorafenib

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Surgical Resection

- Small group of cirrhotics with HCC (<5% of HCC patients) are candidates
- HCC without cirrhosis are also candidates
- Criteria
  - Child-Pugh class A
  - Normal bilirubin
  - Absence of portal hypertension
  - <5 cm in diameter
- 5-year survival rate: 60%-70%
- Tumor recurrence: 50% in 3 years
Survival Following Surgical Resection for HCC


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Transplantation for HCC: Milan Criteria

- 1 lesion ≤ 5 cm
- 3 lesions ≤ 3 cm
- No vascular invasion
- No extrahepatic metastases
Survival and Recurrence-Free Survival Following Liver Transplantation for HCC


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Transplantation for HCC: UCSF Criteria

- Lesion $\leq$ 6.5 cm
- 2-3 lesions
  - largest $\leq$ 4.5 cm
  - total $< 8$ cm diameter
- No vascular invasion
- No extrahepatic metastases

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Survival Following LT for HCC

Yao et al: Liver Transp 8:765, 2002

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Chemoembolization

Hepatocellular carcinoma

Hepatic artery

Ivalon plus
CDDP
Adriamycin
Mitomycin C

Catheter

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HCC: Transarterial Chemoembolization (TACE)

Pre-treatment

Post-treatment

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A 14 gauge needle is directed into the tumor by ultrasound or CT guidance and an alternating current is applied, similar to microwave, Best in tumors less than 5 cm.
HCC: Post RFA Treatment
Management Algorithm for a Solitary HCC nodule

1 lesion < 5 cm

Portal Hypertension
(PLTs < 100K, varices, splenomegaly)
Bilirubin > 1 mg/dl
Child's B/C cirrhosis

NO
Surgical Resection

YES
OLT
Management Algorithm for Early HCC nodule

1 lesion < 5 cm
3 lesions < 3 cm
Absence of Vascular Invasion
Presence of Portal Hypertension

Transplant Candidate

YES
OLT

NO
Ablative Therapies
PEI
RFA
Management Algorithm for Large Solitary or Multicentric HCC

1 lesion > 5 cm
> 3 lesions

Vascular Invasion
Extrahepatic Disease
Systemic Symptoms
(fever, weight loss, night sweats, anorexia...)

NO

TACE

YES

SORAFENIB or other agents
Sorafenib Improves Survival in Hepatocellular Carcinoma: Results of a Phase III Randomized, Placebo-Controlled Trial

Josep M Llovet, Sergio Ricci, Vincenzo Mazzaferro, Philip Hilgard, Jean-Luc Raoul, Stefan Zeuzem, Armando Santoro, Minghua Shan, Marius Moscovici, Dimitris Voliotis, and Jordi Bruix, for the SHARP Investigators Study Group

Supported by Bayer HealthCare and Onyx Pharmaceuticals

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Cellular targets of sorafenib

- VEGF
- PDGFβ
- SCF
- GDNF

Receptor autophosphorylation

Sorafenib

Activation of Raf

Cell survival (anti-apoptotic effects)

Neovascularisation

MEK/ERK

Invasion and metastasis

Tumour cell proliferation


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SHARP: Phase III Study of Sorafenib in HCC

Stratified by macroscopic vascular invasion and/or extrahepatic spread, ECOG PS, geographic region

Patients with advanced HCC, Child-Pugh A, ECOG PS 0-2, at least 1 untreated measurable lesion, and no previous systemic treatment

(N = 602)

Sorafenib
400 mg PO BID
(n = 299)

Placebo
PO BID
(n = 303)

Phase III SHARP Trial

Overall survival (Intention-to-treat)

- **Sorafenib**
  - Median: 46.3 weeks (10.7 mo) (95% CI: 40.9, 57.9)

- **Placebo**
  - Median: 34.4 weeks (7.9 mo) (95% CI: 29.4, 39.4)

Hazard ratio (S/P): 0.69 (95% CI: 0.55, 0.88), \(P=0.00058^*\)

*O’Brien-Fleming threshold for statistical significance was \(P=0.0077\).
Phase III SHARP Trial

Time to Progression (Independent central review)

Hazard ratio (S/P): 0.58  (95% CI: 0.44, 0.74)

\( P = 0.000007 \)

Sorafenib
Median: 24.0 weeks (5.5 mo)
(95% CI: 18.0, 30.0)

Placebo
Median: 12.3 weeks (2.8 mo)
(95% CI: 11.7, 17.1)

Patients at risk
Sorafenib: 299
Placebo: 303

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Summary

• HCC usually arises in cirrhotic liver
• Growth rate varies
• Long asymptomatic phase
• Child-Pugh stage and performance status are important determinants of survival
Conclusions

• Liver transplantation offers best chance for cure in selected cases (preoperative chemoembolization may provide additional benefit)

• Living donor liver transplantation may provide timely transplantation

• Radical (PEI and RFA) therapies are effective for small tumors before OLT
Conclusions

• The role of TACE in non-transplant patients remains to be defined but appears to improve survival

• Sorafenib conferred a survival benefit in unresectable HCC is being studied in multiple patient populations with HCC

• Important to identify patients with end stage liver disease and other high risk groups, particularly Hepatitis B and C carriers as well as NAFL-D in the US