Update on Hepatocellular Carcinoma

Internal Medicine Grand Rounds
July 9th, 2013

Steve Scaglione, M.D.
• Epidemiology

• Pathogenesis

• Surveillance

• Diagnosis

• Staging

• Treatment based on Staging
Epidemiology of Hepatocellular Carcinoma
Primary Liver Cancer: The Global Perspective

Total: 748,300 new cases/year diagnosed and 695,900 deaths/year (2008)

Men:
- Fifth most frequently diagnosed cancer (523,000 cases; 7.9% of all cancers)
- Second leading cause of cancer deaths

Women:
- Seventh most frequently diagnosed Cancer (226,000 cases/year; 6.5% of all cancers)
- Sixth leading cause of cancer deaths

- Jemal et al. Global Patterns of Cancer Incidence and Mortality Rates and Trends. Cancer Epidemiol Biomarkers Prev;19(8); 1893-1907
- El-Serag, H. Epidemiology of Viral Hepatitis and HCC. Gastroenterology. 2012. 142: 1264-1273
Figure 1. Regional Variation in the Estimated Age-Standardized Incidence Rates of Liver Cancer.
The incidence rates shown (numbers of cases per 100,000 persons) pertain to both sexes and all ages. Adapted from the World Health Organization.³
Estimated Liver Cancer Incidence Worldwide in 2008: Men

Globocon. Website. Data from 2008
Estimated Liver Cancer Mortality Worldwide in 2008: Men

Globalcon. Website. Data from 2008
Global Prevalence of HBV and HCV

- El-Serag, H. Epidemiology of Viral Hepatitis and HCC. Gastroenterology. 2012. 142: 1264-1273
HBV/HCV and Attributable Fraction of HCC

THE GLOBAL HEALTH BURDEN OF INFECTION-ASSOCIATED CANCERS IN THE YEAR 2002


<table>
<thead>
<tr>
<th></th>
<th>Liver cancer cases</th>
<th>HBV</th>
<th></th>
<th>HCV</th>
<th></th>
<th>Cases attributable to HBV or HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed countries</td>
<td>110,800</td>
<td>1.6</td>
<td>23.3</td>
<td>26,000</td>
<td>1.3</td>
<td>19.9</td>
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<td>Developing countries</td>
<td>515,300</td>
<td>7.5</td>
<td>58.8</td>
<td>303,000</td>
<td>2.64</td>
<td>33.4</td>
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<tr>
<td>World</td>
<td>626,100</td>
<td>6.3</td>
<td>54.4</td>
<td>340,000</td>
<td>2.4</td>
<td>31.1</td>
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</tbody>
</table>

1Percentage of the general population positive for Hepatitis B surface antigen (HbsAg). 2Percentage of the general population positive for anti Hepatitis C antibody (anti-HCV).
Alcohol, Viral Hepatitis and HCC

- El-Serag, H. Epidemiology of Viral Hepatitis and HCC. Gastroenterology. 2012. 142: 1264-1273
Gender Disparity of HCC

- Consistent across risk factors
- Androgen or androgen w/ HBV
- Androgen receptor
  - Expression
  - Gene polymorphism
- Estrogen/Progesterone
- Fat distribution

El-Serag, H. Epidemiology of Viral Hepatitis and HCC. Gastroenterology. 2012. 142: 1264-1273
Aflatoxin B1 and HCC

• Aflatoxin B1
  – Mycotoxin produced by Aspergillus
  – Grows on foods (ie corn/peanuts) stored in warm, damp conditions
  – Once ingested → AFB1-exo-8,9-epoxide
    • Binds/damages DNA → tumor suppressor p53
    • 30-60% of cases of HCC found in endemic areas
  – International Agency for Research on Cancer
    • Carcinogen
  – Effect is modified by Chronic HBV infection

• El-Serag, H. Epidemiology of Viral Hepatitis and HCC. Gastroenterology. 2012. 142: 1264-1273
• Qian GS. Follow-up study of urinary markers of aflatoxin exposure and liver cancer in China. CEBP 1994; 3:3-10
Epidemiology of HCC in the USA

- 20,000 cases/year
- Past 35yrs, IR has tripled
- Fastest growing Cancer in the US
- 5 year survival - 12%

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

EL-Serag, H. Hepatocellular Carcinoma. NEJM. 2010
Risk Factors for HCC

• All causes of Cirrhosis – **Annual Incidence 3-5%**
  – Alcoholic liver disease
  – Hepatitis C
  – Non Alcoholic Fatty Liver Disease (NAFLD)
  – Inherited metabolic liver disease
    • Hemochromatosis
    • Alpha 1 antitrypsin deficiency
    • Glycogen storage disease
    • Autoimmune hepatitis

• Hepatitis B
  – Cirrhosis - **Annual Incidence 3-5%**
  – Non Cirrhotic – **Annual Incidence 0.2%**
FIGURE. Hepatocellular carcinoma incidence rate,* by sex — United States, 2001–2006
Projected HCV Incidence & Prevalence
Hepatitis C and risk of Cirrhosis

- HCV Infection
- Chronic Hepatitis C
- Cirrhosis
- HCC

- 100
- 85% (60-95%)
- 15% (10-30%)
- 1-3%/year

25 yrs
Risk Factors for HCC in CHC

- Older Age
- Duration of HCV infection
- Males
- Alcohol
- Obesity and Diabetes
- Co-infection w/ HBV and HIV
- Absence of Antiviral treatment
- Viral genotype 1b?
Regional Variations in Mortality

Mortality Rate/100,000 age-adjusted

<table>
<thead>
<tr>
<th>Mortality Rate/100,000 age-adjusted</th>
<th>States</th>
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<tr>
<td>5.24 to 6.12</td>
<td>(6)</td>
</tr>
<tr>
<td>4.49 to 5.24</td>
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<td>4.28 to 4.49</td>
<td>(5)</td>
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<tr>
<td>4.09 to 4.28</td>
<td>(5)</td>
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<tr>
<td>3.94 to 4.09</td>
<td>(5)</td>
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<tr>
<td>3.75 to 3.94</td>
<td>(6)</td>
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<td>3.50 to 3.75</td>
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<td>3.19 to 3.50</td>
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<td>2.74 to 3.19</td>
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<td>2.21 to 2.74</td>
<td>(4)</td>
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<td>Sparse Data</td>
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**Diabetes and risk of HCC**

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<th>0.2</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>10</th>
<th>Effect</th>
<th>Lower</th>
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<td>Lawson et al. 1986</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td>4.88</td>
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<td>Yu et al. 1991</td>
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<td>Hadziyannis et al. 1995</td>
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<td>Shibata et al. 1997 *</td>
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<td>3.54</td>
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<td>La Vecchia et al. 1997</td>
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<td>Braga et al. 1997</td>
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<td>2.92</td>
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<td>El-Serag et al. 2001</td>
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<td>Lagiou et al. 2002</td>
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<td>Hassan et al. 2002</td>
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<td>Matsuo et al. 2003 *</td>
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<td>Davila et al. 2005</td>
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<td>Fukuda et al. 1993</td>
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<td>Shibata et al. 1997 **</td>
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<td>Matsuo et al. 2003 **</td>
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<td><strong>.51</strong></td>
<td><strong>.38</strong></td>
<td><strong>.69</strong></td>
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</table>
DM and Risk of HCC

El-Serag. Gastroenterology. 2004
Obesity, Mortality and HCC

Figure 1. **Summary of Mortality from Cancer According to Body-Mass Index for U.S. Men in the Cancer Prevention Study II, 1982 through 1998.**

For each relative risk, the comparison was between men in the highest body-mass-index (BMI) category (indicated in parentheses) and men in the reference category (body-mass index, 18.5 to 24.9). Asterisks indicate relative risks for men who never smoked. Results of the linear test for trend were significant (P≤0.05) for all cancer sites.
NAFLD/NASH & Risk of HCC

• Systematic Review 1991-2011
  – 17 Cohort Studies
    • 3 population based, 9 clinic based, 5 natural history
  – 18 Case control and cross sectional
  – 26 Case series

• NAFLD/NASH without cirrhosis – 0-3% over 20 years
• NASH with Cirrhosis had a higher risk
  – 2.4% (7yrs) -12.8% (3yrs)
  – Substantially lower risk versus cohorts with HCV Cirrhosis

White D, Kanwal F. Clinical Gastro & Hep 2012
NAFLD & Risk of HCC

RESULTS SUMMARY

- A total of 17,895 cases of HCC were identified for analysis.
  - Among them 2,863 (16%) HCC were due to confirmed NAFLD without evidence of other etiologies; 1,832 (64%) with cirrhosis and 1,031 (36%) without cirrhosis.
  - Among those without cirrhosis, 18% had steatosis without NASH.

Rahman, R. Abstract #97 AASLD 2012
Coffee and HCC

- An inverse relationship between coffee consumption and HCC exist.
- Meta-analysis through 2007: 6 case-control studies, 4 cohort studies comprising 2260 cases of HCC.
  - All showed inverse relationships.
  - 6 studies showed statistically significant association.
  - Summary relative risk 0.54 for case-control studies & 0.64 for cohort studies.
Pathogenesis of HCC
Hallmarks of Cancers

- EGFR inhibitors
- Cyclin-dependent kinase inhibitors
- Immune activating anti-CTLA4 mAb
- Telomerase Inhibitors
- Selective anti-inflammatory drugs

- Aerobic glycolysis inhibitors
- Sustaining proliferative signaling
- Evading growth suppressors
- Avoiding immune destruction

- Deregulating cellular energetics
- Enabling replicative immortality
- Tumor-promoting inflammation

- Resisting cell death
- Inducing angiogenesis
- Activating invasion & metastasis
- Inhibitors of VEGF signaling

- Proapoptotic BH3 mimetics
- Genome instability & mutation
- PARP inhibitors
- Inhibitors of HGF/c-Met
Molecular Pathogenesis of HCC
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>#/type of Patients</th>
<th># of Mutations</th>
<th>Frequently Mutated Genes</th>
<th>Strengths of study</th>
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<td>Totoki</td>
<td>2011</td>
<td>1; Japanese</td>
<td>63</td>
<td>TP53, AXIN1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; HCC genome sequenced</td>
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<tr>
<td>Tao</td>
<td>2011</td>
<td>1; Taiwanese</td>
<td>201</td>
<td>TP53</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; different stages HCC</td>
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<tr>
<td>Li</td>
<td>2011</td>
<td>10; USA/EU/Asia</td>
<td>429</td>
<td>CTNNB1, TP53</td>
<td>Large validation cohort</td>
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<td>Guichard</td>
<td>2012</td>
<td>24; French</td>
<td>994</td>
<td>CTNNB1, TP53, AXIN1</td>
<td>New B-catenin pathway</td>
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<td>Fujimoto</td>
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<td>27; Japanese</td>
<td>147</td>
<td>TP53, CTNNB1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Large scale WGS</td>
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<td>Sung</td>
<td>2012</td>
<td>88; Chinese</td>
<td>344</td>
<td>TERT1</td>
<td>Advanced HCC</td>
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<td>Huang</td>
<td>2012</td>
<td>10; Chinese</td>
<td>347</td>
<td>TP53</td>
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</table>
Integrative Genomic Identification of Genes on 8p Associated With Hepatocellular Carcinoma Progression and Patient Survival

G1: Good Prognosis: HNRPD, PAQR3, PHF17; DCK
Chromosome 4p

G2: Bad Prognosis: SORBS3, DLC1, CCDC25; ELP3, PROSC; Chromosome 8p
Oncofetal Gene SALL4 in Aggressive Hepatocellular Carcinoma

Kol Jia Yong, B.Sc., Chong Gao, M.D., Ph.D., Joline S.J. Lim, M.B., B.S., Benedict Yan, M.B., B.S., Henry Yang, Ph.D., Todor Dimitrov, Ph.D., Akira Kawasaki, M.D., Ph.D., Chee Wee Ong, M.Sc., Kwong-Fai Wong, Ph.D., Sanghoon Lee, Ph.D., Sharada Ravikumar, M.D., Ph.D., Supriya Srivastava, M.D., Xi Tian, B.S., Ronnie T. Poon, M.B., B.S., Ph.D., Sheung Tat Fan, M.D., D.Sc., John M. Luk, D.Med.Sc., Yock Young Dan, M.B., B.S., Ph.D., Manuel Salto-Tellez, M.D., Li Chai, M.D., and Daniel G. Tenen, M.D.
Prevention of HCC
Prevention of HCC

• HBV vaccination
  – Safe and effective
  – Should be given to all newborns and high-risk individuals
  – Incidence in Taiwan has decreased HCC 65-75%
Prevention of HCC: Treating HBV
Preventing HCC
Treating HBV
Surveillance for HCC
Rationale for Surveillance

Fig. 5 Cumulative survival in different stages HCC patients
Surveillance of HCC: Whom to Screen

Table 3. Groups for whom HCC surveillance is recommended or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated

<table>
<thead>
<tr>
<th>Population group</th>
<th>Threshold incidence for efficacy of surveillance (&gt; .25 LYG)(%/year)</th>
<th>Incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian male hepatitis B carriers over age 40</td>
<td>0.2</td>
<td>0.4-0.6%/year</td>
</tr>
<tr>
<td>Asian female hepatitis B carriers over age 50</td>
<td>0.2</td>
<td>0.3-0.6%/year</td>
</tr>
<tr>
<td>Hepatitis B carrier with family history of HCC</td>
<td>0.2</td>
<td>Incidence higher than without family history</td>
</tr>
<tr>
<td>African/North American Blacks with hepatitis B</td>
<td>0.2</td>
<td>HCC occurs at a younger age</td>
</tr>
<tr>
<td>Cirrhotic hepatitis B carriers</td>
<td>0.2-1.5</td>
<td>3-8%/yr</td>
</tr>
<tr>
<td>Hepatitis C cirrhosis</td>
<td>1.5</td>
<td>3-5%/yr</td>
</tr>
<tr>
<td>Stage 4 primary biliary cirrhosis</td>
<td>1.5</td>
<td>3-5%/yr</td>
</tr>
<tr>
<td>Genetic hemachromatosis and cirrhosis</td>
<td>1.5</td>
<td>Unknown, but probably &gt; 1.5%/year</td>
</tr>
<tr>
<td>Alpha 1-antitrypsin deficiency and cirrhosis</td>
<td>1.5</td>
<td>Unknown, but probably &gt; 1.5%/year</td>
</tr>
<tr>
<td>Other cirrhosis</td>
<td>1.5</td>
<td>Unknown</td>
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</table>
Surveillance for HCC
How to Screen

**AASLD Practice Guideline**

**Management of Hepatocellular Carcinoma: An Update**

Jordi Bruix,¹ and Morris Sherman²

- **2005:** Ultrasound and Alpha-Fetoprotein every 6 months
- **2011:** Ultrasound every 6 months
  - U/S: Sensitivity 65-80%, Spec >90%
  - Cost effective - $2000/tumor found
The Fight over AFP

Journal of Hepatology 2010 vol. 52 | 614–615

Serological Surveillance for hepatocellular carcinoma: Time to quit

M. Sherman*

HEPATOLOGY, March 2011

Alpha-Fetoprotein Should Be Included in the Hepatocellular Carcinoma Surveillance Guidelines of the American Association for the Study of Liver Diseases

Jorge A. Marrero, M.D., M.S.¹
HCC Surveillance Utilization

• 13000 Vets 1998-2005 HCV+ Cirrhotics
  – Only 12% had surveillance in first 3 yrs after dx

• 541 patients with diagnosis of HCC
  – 29% received annual surveillance prior to Dx
Liver Mass in a Cirrhotic

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
        - No
          - Biopsy
        - Yes
    - No
      - Biopsy
Diagnosis of HCC
Biomarkers for HCC

**Table 2.** Diagnostic Values of the Hepatocellular Carcinoma Serum Biomarkers

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
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<tbody>
<tr>
<td>AFP-L3 (36, 38)</td>
<td>61.60</td>
<td>92.00</td>
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<td>DCP (36, 38)</td>
<td>72.70</td>
<td>90.00</td>
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<tr>
<td>AFP (36, 38)</td>
<td>67.70</td>
<td>71.00</td>
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<tr>
<td>AFP-L3+DCP (36, 38)</td>
<td>84.80</td>
<td>97.80</td>
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<td>AFP-L3+AFP (36-38)</td>
<td>73.70</td>
<td>86.60</td>
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<td>DCP+AFP (36, 38)</td>
<td>84.80</td>
<td>90.20</td>
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<tr>
<td>AFP-L3+DCP+AFP (36, 38)</td>
<td>85.90</td>
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<tr>
<td>Osteopontin (53)</td>
<td>95.35</td>
<td>100</td>
</tr>
</tbody>
</table>

- Makarem M. An overview of biomarkers for the diagnosis of HCC
- Makarem M. Diagnostic significance of plasma osteopontin in HCC. Ann Hepatology. 2011
Staging-Guided Treatment

HCC

Stage 0
PS 0, Child-Pugh A

Very early stage (0)
Single < 2 cm.

Early stage (A)
Single or 3 nodules < 3 cm, PS ()

- Single
- Portal pressure/ bilirubin
  - Increased
  - Normal

- 3 nodules ≤ 3 cm
  - Associated disease
    - No
    - Yes

Resection, Liver Transplantation, RFA

Curative treatments
Staging-Guided Treatment

- HCC
  - Stage A - C: 0-2, Child-Pugh A-B
  - Stage D: PS >2, Child-Pugh C
    - Mediate stage (B): multinodular, PS 0
    - Advanced stage (C): portal invasion, N1,M1, PS 1-2
    - Terminal stage (D)

- TACE
- Sorafenib
- Symptomatic treatment
- Palliative treatments
Curative Treatment for HCC
Surgical Resection

• Candidates
  – Non cirrhotic
  – Cirrhotic Childs A, without evidence of portal hypertension
  – Single tumor
  – No size cut off (< 5 cm)
• 5 year survival 50% - 70%
• Recurrence > 70%
  – Recurrence and De novo tumor
Treatment of HCC

• Liver Transplantation
  – Milan Criteria
    • 3 lesions all less than 3cm
    • 1 lesion less than 5cm

• Mazzaferro V. NEJM. 1996
• Bruix J. AASLD Guidelines 2010
Loco-Regional Therapy

- Ablation
Palliative Treatments for HCC
Chemoembolization and Radioembolization

**CONVENTIONAL CHEMOEMBOLIZATION**
- **MECHANISM OF ACTION**: Delivery of a high-dose chemotherapy/ethiodized oil emulsion (yellow) followed by arterial embolization to prevent drug washout and promote tumor ischemia/hypoxia.
- **PARTICLE SIZE**: 300–500 µm

**RADIOEMBOLIZATION**
- **MECHANISM OF ACTION**: Delivery of β-emitting microspheres that provide local, high dose tumor radiation. The radiation affects tissues 2.5–11 mm from the delivered microsphere (green).
- **PARTICLE SIZE**: 20–60 µm

**DRUG-ELUTING BEAD CHEMOEMBOLIZATION**
- **MECHANISM OF ACTION**: Delivery of drug-loaded microspheres that provide local, sustained tumor drug delivery combined with tumor ischemia/hypoxia. The drug distributes up to 0.06 mm from the microspheres (orange).
- **PARTICLE SIZE**: 100–300 µm
Treatment of HCC: Sorafenib

• Pathogenesis of HCC is mediated by Raf-1 and vascular endothelial growth factor (VEGF)

• Sorafenib (Nexavar)
  – Mechanism
    • serine–threonine kinases inhibit Raf-1 and B-Raf
    • tyrosine kinase receptor activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3
  – Inhibits tumor angiogenesis
  – Inhibits tumor-cell proliferation
  – Increases apoptosis
Sorafenib

A. Overall Survival

C. Time to Radiologic Progression

P<0.001

No. at Risk

Sorafenib  299 290 270 249 234 213 200 172 140 111 89 68 48 37 24 7 1 0
Placebo  303 295 272 243 217 189 174 143 108 83 69 47 31 23 14 6 3 0

Months since Randomization

Probability of Survival

Probability of Radiologic Progression

Months since Randomization
## Sorafenib: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Sorafenib (N=297) %</th>
<th>Placebo (N=302) %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Any Event</td>
<td>98</td>
<td>39</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>55</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>30</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>29</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hand foot skin reaction</td>
<td>21</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>
Sorafenib: Hand-Foot Skin Reaction

- Anti-angiogenic events typically occur during the first few weeks of treatment with varying degrees of desquamation

- Management
  - Topical treatment
  - Temporary or permanent dose reduction or suspension

Grade 1
Incidence: 8%

Grade 2
Incidence: 6%

Grade 3
Incidence: 8%
Agents Beyond Sorafenib

**TABLE 1:** Therapies for Advanced HCC Undergoing Development as First- and Second-line Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Design</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line</td>
<td>Sorafenib versus placebo</td>
<td>Phase III: approved (2007)</td>
</tr>
<tr>
<td></td>
<td>Sorafenib versus sunitinib</td>
<td>Phase III: halted (2010)</td>
</tr>
<tr>
<td></td>
<td>Sorafenin versus brivanib</td>
<td>Phase III: failed</td>
</tr>
<tr>
<td></td>
<td>Sorafenib versus linifanib</td>
<td>Phase III: halted (2011)</td>
</tr>
<tr>
<td></td>
<td>Sorafenib ± erlotinib</td>
<td>Phase III: failed</td>
</tr>
<tr>
<td></td>
<td>Sorafenib versus bevacizumab ± erlotinib</td>
<td>Phase II: ongoing</td>
</tr>
<tr>
<td>Second-line</td>
<td>Sorafenib ± doxorubicin</td>
<td>Phase III: ongoing</td>
</tr>
<tr>
<td></td>
<td>Brivanib versus placebo</td>
<td>Phase III: failed</td>
</tr>
<tr>
<td></td>
<td>Ramucirumab versus placebo</td>
<td>Phase III: ongoing</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab ± erlotinib</td>
<td>Phase II: ongoing</td>
</tr>
<tr>
<td></td>
<td>versus placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Everolimus versus placebo</td>
<td>Phase III: ongoing</td>
</tr>
</tbody>
</table>
Summary

• HCC is a major global public health problem affecting developing countries more than developed countries.
• It is largely driven by HBV and HCV epidemic
• The largest risk factor is cirrhosis and HBV
  – Surveillance saves lives!
• The incidence of HCC is rising in the USA
• Genetic studies are beginning to identify new targets for molecular therapeutics
• Early stage HCC can be cured
• Late stage HCC has a poor prognosis