Hepatocellular Carcinoma for NNN Cancer Webinar Series

Brian J McMahon, MD
Liver Disease and Hepatitis Program
Alaska Native Tribal Health Consortium
Disclosures

* None
Outline of Talk

- Epidemiology of Hepatocellular Carcinoma (HCC) in the World, US and American Indian/Alaska Native (AI/AN) Peoples
- Etiologies of HCC
- Risk Factors for HCC
- Prevention of HCC
- Screening (surveillance) for HCC
- Treatment of HCC
Global View of HCC

- Primary liver cancer increased from 437,408 cases in 1990 to 714,600 in 2002
- Incidence and mortality rates
  - Decreasing in areas of high and intermediate incidence, including China and Japan
  - Increasing in low-incidence areas, including the United States and Canada
HCC: Age Standardized Incidence Rates 2005 (Men and Women)
The Incidence and 5-Year Survival of HCC in United States

Hepatocellular carcinoma is increasingly the indication liver transplant listing among HCV infected patients in the United States

Incidence rate ratio* for HCC 1.118 95% CI 1.107 – 1.130; P < .001

Fleming JA et al. The Liver Meeting 2013; Abstract 12

*Adjusted for age and sex
CLD Death Rate Trends in AI/ANs and NHWs: 1999–2009

Age-Specific CLD Death Rate Ratios, AI/ANs:NHWs, Hepatitis B-Related CLD


![Bar graph showing age-specific death rates for Cirrhosis and Hepatocellular Carcinoma among AI/ANs and NHWs. The graph illustrates the rate ratios in various age groups and total population.]
Annual Incidence of HCC in Different Liver Diseases

- **Chronic Hepatitis B**
  - Females >50
  - Males >40
  - HBV with cirrhosis
- **Cirrhosis**
  - Chronic HCV
  - Alcoholic (ALD)
  - NAFLD
  - AIH
  - PBC

Incidence HCC/yr.

- 0.3-0.6%
- 0.2-0.6%
- 3-8%
- 3-6%
- Unknown
- Unknown
- Unknown
- 3-5%

From Bruit & Sherman. AASLD HCC Practice Guideline 2010 at aasld.org
Causes of HCC In Alaska Natives

- Chronic Hepatitis B with or without cirrhosis
- Alaska Native Patients with cirrhosis with following etiologies have been identified:
  - Chronic Hepatitis C
  - Non-Alcoholic Liver Disease
  - Alcoholic liver disease
  - Autoimmune hepatitis
  - Primary Biliary Cirrhosis
Decrease incidence of HBV associated HCC over time p=0.048—unpublished data
Primary Liver Cancer in AI/AN

- Using registries from National Program of Cancer Registries of CDC and SEER Program of NCI linked with IHS enrollment records
- AI/AN Peoples had higher incidence of HCC than non-Hispanic Whites (NHW)
- Incidence rates in males ranged from:
  - 7.3 (95%CI; 3.8-12.6) in East Tribes to 17.2 (95%CI 10.4-26.3) in Alaska
- Incidence in females ranged from:
  - 3.8 (95%CI; 1.2-8.2) in East to 6.9 (95%CI; 3.6-11.6) in Alaska
- Increasing trend in AI/AN but did not reach significance except for Alaska
- AI/AN less likely to be diagnosed with localized HCC except Alaska

Jim et al. Cancer 2008;113 (5 Supp);1244-55
Rates/100,000 Age Adjusted to 2000 Standard US Population

Jim et al. Primary Liver Cancer in AI/AN

Cancer
http://onlinelibrary.wiley.com/doi/10.1002/cncr.23728/full#fig2
Risk Factors for HCC in HBsAg-Positive Carriers

- HBV acquisition at birth or early childhood
- >40 years of age males; > 50 years females
- Cirrhosis > no cirrhosis
- Family History of HCC
- Aflatoxin exposure
- HBeAg-positive carriers
- High HBV DNA level in persons >40 years
- HBV genotype C and F
- HBV precore (decrease), core promoter (increase)
- Co-infection with HCV or HDV
Hepatitis B: Association Between Viral Load and Incidence of HCC

Baseline HBV DNA Level (copies/ml)
- ≥10^6: 13.50%
- 10^5–<10^6: 7.96%
- 10^4–<10^5: 3.15%
- 300–<10^4: 0.89%
- <300: 0.74%

HBeAg negative, normal ALT, no liver cirrhosis at entry (n=2,925)
Chen CJ et al. JAMA. 2006;295:65–73
Risk Factors for HCC in Persons with HCV

- Advanced Fibrosis: Cirrhosis or Bridging Fibrosis
  - Risk is minimal in patients with mild or no fibrosis
- HBV/HCV co-infection
- Other risk factors of weaker quality of evidence
  - HCV + HIV
Other Risk Factors from Case-Control Studies in both HBV and HCV

- Heavy alcohol intake: likely due to synergistic effect on development of cirrhosis
- Tobacco use
- Diabetes and obesity
Mortality from Cancer in Obese US Men (n=900,053)

- Prostate (≥35): 1.34
- Non-Hodgkin’s Lymphoma (≥35): 1.49
- All Cancers (≥40): 1.52
- All Other Cancers (≥30): 1.68*
- Kidney (≥35): 1.70
- Multiple Myeloma (≥35): 1.71
- Gall Bladder (≥30): 1.76
- Colon and Rectum (≥35): 1.84
- Esophagus (≥30): 1.91*
- Stomach (≥35): 1.94
- Pancreas (≥35): 2.61*
- Liver (≥35): 4.52

Calle, NEJM 2003
Diabetes Is Associated with a Two-fold Increase in Risk of HCC

Diabetes
N=173,643

No Diabetes
N=650,620

P<0.0001

El-Serag HB, et al, Gastroenterology 2004
# HCC Risk Factors: Prevalence, Risk Estimates, Attributable Fraction?

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence in general population</th>
<th>Risk estimate of HCC</th>
<th>Current prevalence in HCC cases</th>
<th>Population attributable fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>0.5-1%</td>
<td>20-25</td>
<td>10-15%</td>
<td>5-10%</td>
</tr>
<tr>
<td>HCV</td>
<td>1-2%</td>
<td>20-25</td>
<td>30-60%</td>
<td>20-25%</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>10-15%</td>
<td>2-3</td>
<td>20-30%</td>
<td>20-30%</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>30-40%</td>
<td>1.5-2.5</td>
<td>20-50%</td>
<td>30-40%</td>
</tr>
</tbody>
</table>
Prevention of HCC

- Prevention: HBV vaccination
  - Decrease risk of HCC in childhood in Taiwan, Thailand and Alaska from universal infant/childhood vaccination

- Decrease Risk:
  - Treatment of underlying liver disease
  - Coffee
  - Statins
  - Metformin

- Prolonged survival: Surveillance for HCC
Prevention of or Reduction of Risk for HCC

- Treat underlying cause of cirrhosis or hepatitis
  - Vaccination against HBV
  - Antiviral therapy for HBV for those who meet criteria
    - Lok, McMahon AASLD Guideline for HBV at aasld.org
  - Cure of hepatitis C with Direct Acting Antivirals (DAA)
  - Weight loss/exercise for persons with metabolic syndrome
  - Abstinence for alcoholic cirrhosis
  - Targeted therapy for Autoimmune hepatitis or PBC
Number of Alaska Native Children Under 20 Years of Age who Tested Positive for Hepatitis B: 1988-2008

Figure 2.

Number of Alaska Native Children Under 20 Years of Age who Tested Positive for Hepatitis B: 1988-2008

<table>
<thead>
<tr>
<th>Year</th>
<th>No. HBsAg Positive</th>
<th>% HBsAg+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>450</td>
<td>1.4%</td>
</tr>
<tr>
<td>1993</td>
<td>300</td>
<td>1.2%</td>
</tr>
<tr>
<td>1998</td>
<td>150</td>
<td>1.0%</td>
</tr>
<tr>
<td>2003</td>
<td>100</td>
<td>0.8%</td>
</tr>
<tr>
<td>2008</td>
<td>50</td>
<td>0.6%</td>
</tr>
<tr>
<td>2009</td>
<td>0</td>
<td>0.4%</td>
</tr>
<tr>
<td>2010</td>
<td>0</td>
<td>0.2%</td>
</tr>
<tr>
<td>2011</td>
<td>0</td>
<td>0.0%</td>
</tr>
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</table>
Hepatocellular Cancer in Alaska Native Children <20 Years Old, 1969-2008

Annual Rate per 100,000

year of diagnosis

HCC and Hepatitis C Treatment

### Cumulative Incidence of HCC

<table>
<thead>
<tr>
<th>Year</th>
<th>0 yrs.</th>
<th>5 yrs.</th>
<th>10 yrs.</th>
<th>15 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-SVR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Patients with HCC</td>
<td>0</td>
<td>376</td>
<td>164</td>
<td>56</td>
</tr>
<tr>
<td>Patients at risk</td>
<td></td>
<td></td>
<td>1.2%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Cumulative incidence 0%</td>
<td></td>
<td></td>
<td></td>
<td>3.3%</td>
</tr>
<tr>
<td>Non-SVR</td>
<td>980</td>
<td>723</td>
<td>345</td>
<td>141</td>
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<tr>
<td>Cumulative incidence 0%</td>
<td>3.6%</td>
<td>10.9%</td>
<td>15.5%</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>0 yrs.</th>
<th>5 yrs.</th>
<th>10 yrs.</th>
<th>15 yrs.</th>
</tr>
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<tr>
<td><strong>SVR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with HCC</td>
<td>0</td>
<td>7</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Patients at risk</td>
<td>121</td>
<td>67</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Cumulative incidence 0%</td>
<td>6.0%</td>
<td>11.0%</td>
<td>11.0%</td>
<td></td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Year</th>
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<th>10 yrs.</th>
<th>15 yrs.</th>
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<tr>
<td><strong>Non-SVR</strong></td>
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<td></td>
</tr>
<tr>
<td>SVR</td>
<td>0</td>
<td>46</td>
<td>61</td>
<td>64</td>
</tr>
<tr>
<td>Patients with HCC</td>
<td>0</td>
<td>376</td>
<td>179</td>
<td>43</td>
</tr>
<tr>
<td>Patients at risk</td>
<td></td>
<td></td>
<td>14.1%</td>
<td>25.5%</td>
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<tr>
<td>Cumulative incidence 0%</td>
<td></td>
<td></td>
<td>25.5%</td>
<td>31.1%</td>
</tr>
</tbody>
</table>
Impact of HBV Treatment on HCC

- Randomized controlled trial comparing lamivudine versus placebo
- Patients with advanced fibrosis or cirrhosis
- HBV-DNA (>10^5 copies/mL) or HBeAg+
- Study terminated prematurely by DSMB (median Tx=32.4 mo)

AASLD Recommendations for Screening for HCC

* Surveillance for HCC should be performed using ultrasonography (level II).
* Patients should be screened at 6 month intervals (level II).
* The surveillance interval does not need to be shortened for patients at higher risk of HCC (level III).

From Bruit & Sherman. AASLD HCC Practice Guideline 2010 at aasld.org
HCC Surveillance: Randomized Controlled Trials

- Cirrhosis (NONE)
- Hepatitis C infection (NONE)
- Hepatitis B infection carriers
  - China
  - Two trials
  - One showed benefit  (Zhang et al. 2004)
  - One did not show benefit  (Chen et al. 2003)
Surveillance for HCC Reduces Mortality:
A Randomized Controlled Trial of AFP+US q 6 months

Ultrasound Surveillance in Early HCC: Systematic Review

Study

- Surveillance every 6 months or less
  - Kobayashi 1985: 0.50 (0.15, 0.85)
  - Oka 1900: 0.68 (0.53, 0.82)
  - Pateron 1904: 0.23 (0.00, 0.46)
  - Cottone 1994: 0.87 (0.75, 0.99)
  - Zoli 1996: 0.91 (0.82, 1.01)
  - Henrion 2000: 0.67 (0.29, 1.04)
  - Bolondi 2001: 0.82 (0.72, 0.92)
  - Subtotal ($I^2 = 83.6\%, P = 0.000$): 0.70 (0.56, 0.85)

- Surveillance 6–12 months
  - Arrigon 1998: 0.69 (0.46, 0.91)
  - Tradati 1998: 0.33 (−0.04, 0.71)
  - Santagostino 2003: 0.25 (−0.05, 0.55)
  - Sangiovanni 2004: 0.50 (0.41, 0.60)
  - Sangiovanni 2006: 0.50 (0.38, 0.62)
  - Subtotal ($I^2 = 33.8\%, P = 0.196$): 0.50 (0.40, 0.59)

Singal A, et al. APT 2009
AFP & HCC

- AFP as a serologic marker has a low sensitivity and specificity for HCC
- AFP can be elevated by active liver inflammation and regeneration
- Persons with AFP elevation are at higher risk of developing HCC in future
- AFP has a high negative predictive value for the absence of HCC (AFP <8ng/ml) but a low positive predictive factor
ANTHC LDHP Program Recommendations for Screening for HCC in Chronic HBV

- AFP every 6 months for all persons
- US also every 6 months for those
  - Cirrhosis
  - Family History of HCC
  - Previous HCC diagnosis
  - Men >40 and women > 50 years who live in community with US available
- If AFP > 10mg/ml, then do US initially and if negative, repeat AFP & US in 3 months then every 3-6 months thereafter
Other Surveillance Considerations to Detect HCC in HBV

* Persons for whom liver Ultrasound should be performed if living in a community that has US available
  * All Males over 40 years of age
  * All Females over 50 years of age
  * Persons with HBV genotype C over 40 years of age*
  * Persons infected with HBV genotype F at any age*
  * Persons over age 40 with high viral load (>20,000 IU/ml)

Increase risk of HCC in HBV genotypes C and F in Alaska Native Persons
Livingston: J Infectious Diseases 2007;195:5-11
ANTHC LDHP Program Recommendations for Screening for HCC other than HBV

- Patients with cirrhosis from HCV, NAFLD, ALD, AIH, PBC or other cause
  - AFP and US every 6 months
- Patients with HCV in whom liver fibrosis stage is unknown
  - AFP every 6 months
  - If AFP > 10, do US initially and repeat AFP US in 3 months then every 3-6 months thereafter
Effectiveness of Surveillance for HCC in Alaska Native Persons

- Chronic HBV: Hepatology 2000;32:842-6
  - Sensitivity of AFP >15ng/ml: 97%
  - Specificity excluding pregnancy: 95%
  - Positive Predictive value: 31%
  - Significant 5 yr. survival compared to prior to 1982 when no screening done
- 53 cases detected since 1982
  - 47 (89%) detected at potentially curable stage
    - 34 resected
    - 13 treated ETOH injection or RFA
HCC and AFP in Alaska Natives with Chronic HCV

- Effectiveness of AFP to use to determine who needs liver ultrasound additionally
  - No patient with AFP persistently <8ng/ml developed HCC over 6 year period
  - AFP >8mg/ml had a 39% sensitivity and 95% specificity of detecting advanced fibrosis (Ishak 3-6 = bridging fibrosis or cirrhosis)
  - Persons with ESLD or HCC had 158 times the odds of having AFP >8ng/ml (95%CI 37-691)

Diagnosis of HCC

* Barcelona Criteria:
  * Two imaging studies with compatible lesion
    * Hypoechoic lesion on US
    * Lesion that lights up on arterial phase of tri-phasic or Quadra-phasic CT
      * Don’t order non-contrast/contrast CT for HCC: you’ll miss many small lesions
    * Compatible lesion on MRI with Gadolinium
  * One compatible image plus an AFP >400 mg/ml
Quadra-Phasic CT for Hepatocellular Carcinoma

- Baseline scan
- Arterial phase
- Portal venous phase
- Delayed phase

Washout Phase
Diagnostic algorithm for suspected HCC.

From Bruit & Sherman. AASLD HCC Practice Guideline 2010 at aasld.org
Hepatocellular Carcinoma: Treatment

Very early stage
1 HCC <2 cm
Carcinoma in situ

Early stage
1 HCC or 3 nodules
<3 cm, PS 0

Intermediate stage
No portal vein thrombosis
Multinodular, PS 0

Advanced stage
Portal invasion
Metastases, PS 0-2

Terminal stage

1 HCC
Portal pressure / bilirubin
Normal
Resection

3 nodules <3 cm
Associated diseases

Normal
Resection

OLT
PEI / RFA

Chemo-embolization

Sorafenib

Potentially curative treatments
Palliative treatments
Symptomatic Therapy

The BCLC staging system for HCC

RFA electrode
RFA generator
Hepatocellular Carcinoma: Treatment
Randomized Trial of RFA versus Resection for Very Early HCC

- Study Groups: RFA = 71; Resection = 90
- No difference among groups in terms of liver function, performance status and tumor burden (all < 3 cm)
- No difference in overall survival
- RFA had less morbidity and complications

Hepatocellular Carcinoma: Treatment
Transplantation (LT)

- Curative for HCC and chronic liver disease
- MELD exception points for HCC
- Live donor LT considered for HCC progression outside MILAN criteria
- UCSF criteria not implemented in current MELD exception allocation policy

Survival

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1 year</td>
<td>91%</td>
</tr>
<tr>
<td>2 year</td>
<td>75%</td>
</tr>
<tr>
<td>5 year Milan</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>5 year (extended)</td>
<td>~50%</td>
</tr>
</tbody>
</table>

### Sensitivity Meta-Analysis of Core RCTs Reporting 1 or 2-year Survival with Chemoembolization / Embolization: Various Treatment Comparisons

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Patients</th>
<th>Favors Treatment</th>
<th>Favors Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment vs no treatment</td>
<td>367</td>
<td></td>
<td></td>
<td>0.022</td>
</tr>
<tr>
<td>High quality trials</td>
<td>440</td>
<td></td>
<td></td>
<td>0.039</td>
</tr>
<tr>
<td>Chemoembolization vs control</td>
<td>323</td>
<td></td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>Embolization vs control</td>
<td>215</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Treatment vs control:</td>
<td>545</td>
<td></td>
<td></td>
<td>0.051</td>
</tr>
<tr>
<td>1 year survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Llovet JM, Bruix J. Hepatology 2003; 37:429
Patients at risk:

Sorafenib:
- 299
- 274
- 241
- 205
- 161
- 108
- 67
- 38
- 12
- 0

Placebo:
- 303
- 276
- 224
- 179
- 126
- 78
- 47
- 25
- 7
- 2

Survival Probability

Hazard ratio (Sorafenib/Placebo): 0.69 (95% CI, 0.55-0.87)
P = 0.00058*

Phase III SHARP Trial: Overall Survival (Intent-to-Treat Population)

*S'Orien-Fleming threshold for statistical significance was P = 0.0077; CI=confidence interval

Llovet JM et al. NEJM. 2008; 359(4):378
Problems with Sorafenib

- Survival benefit: <3.5 months
- Cost: > $70,000
- Side effects: Many patients can’t tolerate; can result in poor quality of life for remainder of time patient has, especially if it doesn’t work
- While it is on our formulary, our oncologists and our Hepatology service have stopped using it as every patient treated asked to stop
Conclusions

* Incidence of HCC is rising in US
  * Etiologies of HCC have changed in last 20 yrs.
* New risk factors for HCC in HBV have been identified
* Surveillance for HCC in HBV with AFP alone is effective 1\textsuperscript{st} step in detection but US should also be used if available
* AFP is also a surrogate marker for advanced fibrosis in HCV
* Better serologic screening tests for HCC are needed
LiverConnect Videoteleconference

- 1\textsuperscript{st} Tuesdays, 8-9am Alaska Standard Time
- Case study presentations from rural providers
- CEUs (1.0 for each session)
- Contact Ebba Paniptchuk to join: +1 907-729-1560
- Questions: Email liverconnect@anthc.org or contact Julia Plotnik, RN +1 907-729-1581 or Jim Gove, RN +1 907-729-1568
Liver Disease/Hepatitis Program Website

http://www.anthctoday.org/community/hep/index.html

- Initial Funding from Government
- Reviewed quarterly by our advisory group of indigenous patients living with HCV
- Contents of Website
  - Patient Information
  - Provider Information
  - Hepatitis C Treatment
  - Publications
  - LiverConnect – Past presentations
  - The website is constantly updated as new treatments