Hepatitis C and Liver Cancer: What’s the Link – Identify, Treat and Prevent

Moises Ilan Nevah, MD
Assistant Professor of Medicine and Surgery
UTHealth McGovern Medical School
Division of Gastroenterology, Hepatology and Nutrition
Center for Abdominal Transplantation and Regenerative Medicine
Hepatocellular Carcinoma
Hepatocellular Carcinoma (HCC)

A primary malignancy of the liver that most always occurs in persons with underlying liver disease
Malignant Transformation – Multistep Process

Normal liver → Chronic Injury or Inflammation → Liver cirrhosis → Epigenetic alterations, Genetic alterations, Dysplastic nodules[1]
HCC – Is it Important?

- 5th most common type cancer
  - Approx. 750,000 cases per year worldwide
- 3rd most common cause of cancer mortality
  - > 600,000 deaths annually
- Distribution worldwide follows HBV & HCV infection
  - 84% of infections are in developing countries
  - Subsaharan Africa, Middle East and SE Asia are areas of endemic infection
  - HCC is the leading cause of cancer death in Asia & Middle East
- Incidence is increasing in the U.S.
  - Incidence has tripled in the last three decades – 36,000 cases expected this year
- Alarming increase in parts of Texas
The Incidence and 5-Year Survival of HCC in US

HCC is increasing in Texas in the last 5 yrs.
Texas HCC Incidence **Doubled** in the Past 15 yrs
South Texas – Highest Incidence of HCC

Age-adjusted Rate per 100,000 population

US 7.7
Texas 9.1
South Texas 16.3
Comparison of Hepatocellular Carcinoma in Men in the South Texas Region

- Hispanics in the 38 South Texas Counties have a significantly higher incidence rate of HCC than Hispanics in the remainder of Texas (216 counties) and Hispanics in the US (SEER)
- Non-Hispanic whites in South Texas have a significantly higher rate than non-Hispanic whites in the US (SEER)

Hepatocellular Carcinoma Incidence, Men, 2006-2010, South Texas Compared to the Rest of Texas and the US (SEER) by Race/Ethnicity

Rates are per 100,000 and age-adjusted to the 2000 US Standard Population (19 age groups - Census P25-1130) standard.
# HCC in the US: Effect of Immigration

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Hispanic Native</td>
<td>13</td>
<td>8.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Hispanic Immigrant</td>
<td>6.9</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Asian Native</td>
<td>6.7</td>
<td>4.9</td>
<td>6.1</td>
</tr>
<tr>
<td>Asian Immigrant</td>
<td>18.3</td>
<td>17.9</td>
<td>13.8</td>
</tr>
</tbody>
</table>
HCC Mortality is Increasing in Texas in Past 5-yrs Compared to Other Cancers

![Diagram showing 5-Year Rate Changes - Mortality, Texas, 2007-2011: All Ages, Both Sexes, All Races (incl Hisp)]

Source: Death data provided by the National Vital Statistics System public use data file. Death rates calculated by the National Cancer Institute using SEER*Stat. Death rates (deaths per 100,000 population per year) are age-adjusted to the 2000 US standard population (19 age groups: <1, 1-4, 5-9, …, 80-84, 85+). Population counts for denominators are based on Census populations as modified by NCI. The 1999-2012 US Population Data File is used with mortality data. Please note that the data comes from different sources. Due to different years of data availability, most of the trends are AAPCs based on APCs but some are EAPCs calculated in SEER*Stat. Please refer to the source for each graph for additional information.

# - The annual percent change is significantly different from zero (p<0.05).
Most HCC patients are diagnosed at late stages

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Localized</td>
<td>42%</td>
<td>28%</td>
<td>33%</td>
<td>44%</td>
<td>67%</td>
</tr>
<tr>
<td>Regional</td>
<td>28%</td>
<td>22%</td>
<td>28%</td>
<td>29%</td>
<td>39%</td>
</tr>
<tr>
<td>Distant</td>
<td>18%</td>
<td>22%</td>
<td>19%</td>
<td>17%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Altekruse et al, Hepatology 2012
Ultrasound can be efficacious for early HCC detection

Singal et al. Aliment Pharm Ther 2009
Surveillance associated with early HCC detection in patients with cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trevisani 2002</td>
<td>2.10 (1.80 - 2.46)</td>
</tr>
<tr>
<td>Van Vlierberghe 2005</td>
<td>1.92 (1.29 - 2.86)</td>
</tr>
<tr>
<td>Ando 2006</td>
<td>2.84 (2.20 - 3.65)</td>
</tr>
<tr>
<td>Tanaka 2006</td>
<td>1.71 (1.48 - 1.99)</td>
</tr>
<tr>
<td>Leykum 2007</td>
<td>4.43 (2.69 - 7.27)</td>
</tr>
<tr>
<td>Gellert 2007</td>
<td>2.17 (1.25 - 3.75)</td>
</tr>
<tr>
<td>Stravitz 2008</td>
<td>2.62 (1.88 - 3.66)</td>
</tr>
<tr>
<td>Silveira 2008</td>
<td>0.84 (0.43 - 1.63)</td>
</tr>
<tr>
<td>Kuo 2010</td>
<td>2.56 (2.27 - 2.90)</td>
</tr>
<tr>
<td>Tong 2010</td>
<td>2.57 (1.64 - 4.02)</td>
</tr>
<tr>
<td>Noda 2010</td>
<td>2.00 (1.61 - 2.48)</td>
</tr>
<tr>
<td>Jou 2010</td>
<td>1.86 (1.47 - 2.36)</td>
</tr>
<tr>
<td>Zapata 2010</td>
<td>2.62 (1.55 - 4.44)</td>
</tr>
<tr>
<td>Tong 2010</td>
<td>3.20 (1.70 - 6.04)</td>
</tr>
<tr>
<td>Stroffolini 2011</td>
<td>3.10 (1.90 - 5.20)</td>
</tr>
<tr>
<td>Yang 2011</td>
<td>2.97 (2.27 - 3.89)</td>
</tr>
<tr>
<td>Kallwitz 2011</td>
<td>2.28 (1.64 - 3.17)</td>
</tr>
<tr>
<td>Reau 2011</td>
<td>2.64 (1.77 - 3.93)</td>
</tr>
<tr>
<td>Miguel 2012</td>
<td>1.48 (1.07 - 2.05)</td>
</tr>
<tr>
<td>Ayala 2012</td>
<td>1.15 (0.80 - 1.67)</td>
</tr>
<tr>
<td>Sarkar 2012</td>
<td>4.15 (2.02 - 8.54)</td>
</tr>
<tr>
<td>Singal 2013</td>
<td>0.99 (0.67 - 1.47)</td>
</tr>
</tbody>
</table>

**Pooled Relative Risk of Early Detection**  
(I-squared = 78.5%)  
2.08 (1.79 - 2.37)
Surveillance associated with survival benefit in patients with cirrhosis

N=370 surveillance HCC vs. 450 incidental HCC
Surveillance associated with survival benefit in patients with cirrhosis

Survival rate (%)

Log rank test $p < 0.001$

Number at risk
- Surveillance: 279, 123, 57, 24, 6
- Non-surveillance: 720, 216, 86, 43, 8

Survival (n=295) vs. other (n=779)
- Tumor size: 2.7 vs. 6.0 cm
- Early stage HCC: 61% vs. 21%
- Curative treatment: 57% vs. 32%
Surveillance is cost-effective in patients with cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Cost-effective Surveillance Strategy</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin 2004</td>
<td>Child A cirrhosis</td>
<td>US and AFP q6 months</td>
<td>$28703</td>
</tr>
<tr>
<td>Thompson 2007</td>
<td>Child A cirrhosis</td>
<td>AFP triage q6 months</td>
<td>£30,400</td>
</tr>
<tr>
<td>Andersson 2008</td>
<td>Child A cirrhosis</td>
<td>US q6 months</td>
<td>$30,700</td>
</tr>
</tbody>
</table>
Why Is Liver Cancer Increasing?

• Liver cancer is increasing because cirrhosis is increasing

• Cirrhosis is increasing because
  • There are a lot of baby boomers
  • They have a high prevalence of hepatitis C
  • They are getting older
  • They are getting fatter
### HCC Risk Factors

<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>
Hepatitis C
HCV Epidemiology 101: Worldwide burden of disease is increasing

• WHO estimates 130 – 170 million people, (3% of world’s population) HCV infected and at risk of cirrhosis / HCC

• There are 3 – 4 million new infection / yr.

• HCV is responsible for 50 - 75% of all HCC and 50 – 60% of all liver transplants in the developed world

• HCV associated cirrhosis leads to liver failure and death in about 20 – 25% of cirrhotic patients
Natural History of Hepatitis C

- Normal Liver
- Chronic Hepatitis
- Cirrhosis

HCV Infection: 75-85% chance of progressing to Chronic Hepatitis
20-30% chance of progressing to Cirrhosis
2-7% per year risk of developing HCC or ESLD

Time (years): 0, 10, 20, 30
World distribution of HCV per genotype
Baby Boomers (1945–1965) Account for 76.5% of HCV in the US

An estimated 35% of undiagnosed baby boomers with HCV currently have advanced fibrosis (F3-F4; bridging fibrosis to cirrhosis)³

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Who Should Be Tested for HCV

**CDC Recommendations**

- Everyone born from 1945 through 1965 (one-time)
- Persons who ever injected illegal drugs
- Persons who received clotting factor concentrates produced before 1987
- Chronic (long-term) hemodialysis
- Persons with persistently abnormal ALT levels.
- Recipients of transfusions or organ transplants prior to 1992
- Persons with recognized occupational exposures
- Children born to HCV-positive women
- HIV positive persons

**USPSTF Grade B Recs**

- Everyone born from 1945 through 1965 (one-time)
- Past or present injection drug use
- Sex with an IDU; other high-risk sex
- Blood transfusion prior to 1992
- Persons with hemophilia
- Long-term hemodialysis
- Born to an HCV-infected mother
- Incarceration
- Intranasal drug use
- Receiving an unregulated tattoo
- Occupational percutaneous exposure
- Surgery before implementation of universal precautions

*Pertains to persons with normal liver enzymes; if elevated liver enzymes need HBV and HCV testing

Horrible job identifying patients and linking care
3 of 5 Patients With HCV Are Undiagnosed

**SCREENING BARRIERS**

- Lack of public awareness of risk factors
- Lack of routine risk assessment by many PCPs
- Patient reluctance to admit risk factors
  - *No risk factors identified in 69% of cases*
- Infected individuals often asymptomatic
- Liver panels/serologies currently triggered by $\uparrow$ALT


*Mortality Rates = HBV, HCV, HIV listed as cause of death
Because of decedent can have multiple causes of death, a record listing more than 1 type of infection was counted for each type of infection
Forecasted Annual Deaths Associated with HCV
Incidence of Acute HCV by Age group

Reported cases/100,000 population

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)
Texas 2016: Presenting to their primary care physician with a new Dx of HCV already have cirrhosis

38%
Number of Newly Reported HCV Cases, Houston, TX

*The 2014 data is incomplete (as of 12/10/2014)
Finding Younger HCV Patients

• City Health Department provides the largest number of STD screenings in the city through its 3 city-wide STD clinics, mobile unit, and 6 community-based partners.

• Utilizing existing HIV service linkage infrastructure and staff to link HCV RNA positive patients to care.

• Central city laboratory provides HCV RNA testing.

• STD clinics now operational with electronic medical record system, facilitating screening.

QUICK FACTS
• Integrated STD screening, including HIV and HCV.
• Implemented at 3 city-wide STD clinics and one mobile clinic.
• Providing follow-up RNA confirmatory on all HCV screening tests.

RESULTS
Since implementing integrated screening at all city STD clinics and community-based testing sites:
• Conducted over 1,065 HCV Ab tests.
• Identified 89 HCV Ab+ patients (6.8%); of those with an RNA test, 30% chronic cases.
• Majority of Ab+ patients are younger than the birth cohort.
• 95% male; 70% African American

CONCLUSION
• Screening at STD clinics and using existing HIV service linkage structure is an efficient way to reach HCV patients, especially those younger than the birth cohort.
• To make screening sustainable, central lab will move to fee scale for screening and RNA to community agencies and individuals.

Nearly 70% of all Ab+ are younger than 48
6.8% prevalence for HCV

Who should be treated?

1. Hepatitis C infection **IS CURABLE**
2. **ALL** HCV infected patients **SHOULD** receive treatment
3. Groups that should receive immediate therapy as they will derive the highest benefit
   a. Patients with a diagnosis of cirrhosis
   b. Liver Transplant recipients with active viremia
   c. HCV/HIV coinfected patients
   d. Extrahepatic manifestations of HCV
      - Cryoglobulinemia
      - B-cell Lymphoma
      - Porphyria
Who should be treated

• Special considerations to the following population groups
  1. Prison inmates
  2. HCV/HIV men who have sex with men
  3. Clinicians at high risk of transmission to patients
  4. IVD users
**SVR-12 = Cure** in Genotype 1 treatment naïve

<table>
<thead>
<tr>
<th>MEDICATIONS</th>
<th>SVR-12 rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir + Sofosbuvir</td>
<td>94 – 99 %</td>
</tr>
<tr>
<td>Simeprevir + Sofosbuvir</td>
<td>91 – 94%</td>
</tr>
<tr>
<td>Ombitasvir + Paritaprevir + Dasabuvir + Ribavirin</td>
<td>91 – 100 %</td>
</tr>
<tr>
<td>Sofosbuvir + Daclatasvir</td>
<td>90 – 100 %</td>
</tr>
<tr>
<td>Elbasvir + Grazoprevir</td>
<td>94 – 100%</td>
</tr>
</tbody>
</table>

## HCV Treatment Price Tag

<table>
<thead>
<tr>
<th>Regimen^ and Duration of Therapy</th>
<th>Cost of Regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir + Sofosbuvir x 12 weeks</td>
<td>$147,000</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir x 24 weeks</td>
<td>$294,000</td>
</tr>
<tr>
<td>Elbasvir-Grazoprevir x 12 weeks</td>
<td>$54,600</td>
</tr>
<tr>
<td>Elbasvir-Grazoprevir x 16 weeks</td>
<td>$72,800</td>
</tr>
<tr>
<td>Ledipasvir-Sofosbuvir x 12 weeks</td>
<td>$94,500</td>
</tr>
<tr>
<td>Ledipasvir-Sofosbuvir x 24 weeks</td>
<td>$189,000</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir x 12 weeks</td>
<td>$84,000</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir x 24 weeks</td>
<td>$168,000</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir x 12 weeks</td>
<td>$150,000</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir x 24 weeks</td>
<td>$300,000</td>
</tr>
</tbody>
</table>
Curing HCV reduces the incidence of HCC

Note: Even when HCV is Cured you still need to continue screening!
Summary

1. Hepatitis C is the leading cause of cirrhosis, HCC and liver transplantation
2. The incidence and mortality associated with HCV and HCC is increasing in US and specially in Texas.
3. We are doing a poor job in identifying and screening patients for Hepatitis C. And linkage to care is suboptimal
4. Hepatitis C is CURABLE. Treatment although expensive, is cost effective and decreases liver related complications