Epidemiology Trends: Evolving Etiologies and Risk Factors and Screening Guidelines for Populations at Risk

Tamar H. Taddei, MD
Disclosures:

None relevant to this talk
Objectives

• Learn about the shifting trends in the epidemiology of HCC
• Understand the risk factors for HCC
• Appreciate the importance of “screening” (surveillance)
• Explore tools that may refine our approach to surveillance
HCC: An Epidemic...

• Hepatocellular carcinoma is rising in incidence globally, and tripled in the US in over the last three decades
• HCC is the leading cause of death in cirrhosis
• 5th most common cancer in men worldwide, 2nd leading cause of cancer death (841,080 new cases and 781,631 deaths predicted in 2018)

Mittal *J Clin Gastro* 2013; Ryerson *Cancer* 2016; Bray *Cancer* 2018
2018 GLOBOCAN estimates of incidence and mortality worldwide for Liver Cancer

Diagram showing age-standardized incidence rate per 100,000 for males and females across different regions.
HCC is Unique

- 1 patient, 2 diseases
  - Cirrhosis leads to
    - multifocal liver cancer
    - high recurrence rates
  - Cirrhosis complicates treatment and trial design
- HCC can be diagnosed by imaging alone
- HCC is the only solid organ malignancy for which transplantation offers a cure
RISK FACTORS
Risk Factors for HCC

- Chronic HBV (5-100 fold ↑ risk)
  - 0.02-0.20 (per 100 person-years) carriers
  - 0.3-0.6 in chronic HBV without cirrhosis
  - 2.2-3.7 in chronic HBV with cirrhosis

- HCV infection (15-20 fold ↑ risk)
  - Advanced fibrosis/cirrhosis, 25-30 yr latency
  - annual rate of developing HCC: 1% to 7%

Risk Factors for HCC

• Alcoholic cirrhosis
  • Second to HCV in the USA

• No clear etiology for 30–40% of cases in the West
  • NAFLD and the metabolic syndrome
  • 1.5–2.0-fold ↑ risk among obese
  • diabetes associated with a 2-fold ↑ risk

• \textit{AGE} is a risk factor for all cancers…

Prevalence of Obesity Not Entirely to Blame…

United States Centers for Disease Control.
Available at: https://www.cdc.gov/obesity/data/prevalence-maps.html
Age-adjusted incidence of HCC in the US

Kulik, El-Serag Gastroenterology 2019
White Gastroenterology 2017
“SCREENING” (SURVEILLANCE) GUIDELINES
Routine Surveillance Recommended in High-risk Populations

- All patients with cirrhosis with US +/- AFP q 6 mos (AASLD)
- All patients with HCV with advanced fibrosis/cirrhosis (stage 3 and 4) (AASLD/IDSA)
- Non-cirrhotic patients with chronic hepatitis B
Non-Cirrhotic HBV Carriers at Risk: A Global Concern

- Asian males > 40
- Asian females > 50
- Africans > 20
- Family history of HCC

• Lifetime risk 10-25%
• 35-87 million will die

http://globocan.iarc.fr/old/FactSheets/cancers/liver-new.asp
https://www.cdc.gov/globalhealth/immunization/othervpds/preventing_hepatitisb.html
5-Year Survival Is Substantially Higher When Liver Cancer Is Caught Early…

Percent of Cases by Stage

- Localized: 44%
- Regional: 27%
- Distant: 18%
- Unknown: 12%

5-Year Relative Survival

- Localized: 31.3%
- Regional: 10.6%
- Distant: 2.4%
- Unknown: 6.3%

National Cancer Institute.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N of participants (studies)</th>
<th>Overall quality of evidence</th>
<th>Relative effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early tumor detection rate</td>
<td>10,904 (38 observational studies)</td>
<td>Ⓞⓥ⓷⓴  LOW</td>
<td>OR 2.11 (1.88 to 2.33)</td>
</tr>
<tr>
<td>Early tumor detection rate (using BCLC to define early stage)</td>
<td>6,348 (23 observational studies)</td>
<td>Ⓞⓥ⓷⓴  LOW</td>
<td>OR 2.08 (1.80 to 2.37)</td>
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<tr>
<td>Early tumor detection rate (using BCLC to define early stage)</td>
<td>6,573 (6 observational studies)</td>
<td>Ⓞⓥ⓷⓴  LOW</td>
<td>OR 1.96 (1.41 to 2.73)</td>
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<td>Curative treatment rate</td>
<td>24,374 (34 observational studies)</td>
<td>Ⓞ⓷⓷①* MODERATE</td>
<td>OR 2.24 (1.99 to 2.52)</td>
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<tr>
<td>3-year survival rate*</td>
<td>10,850 (23 observational studies)</td>
<td>Ⓞ⓷⓷①* MODERATE</td>
<td>OR 1.90 (1.67 to 2.17)</td>
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<tr>
<td>Early detection (ultrasound only)</td>
<td>(5 observational studies)</td>
<td>Ⓞ⓷⓴  LOW</td>
<td>OR 2.04 (1.55 to 2.68)</td>
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<tr>
<td>Early detection (ultrasound +/- AFP)</td>
<td>(14 observational studies)</td>
<td>Ⓞ⓷⓴  LOW</td>
<td>OR 2.16 (1.80 to 2.60)</td>
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<tr>
<td>Receipt of curative treatment (ultrasound only)</td>
<td>(8 observational studies)</td>
<td>Ⓞ⓷⓴  LOW</td>
<td>OR 2.23 (1.83 to 2.71)</td>
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<tr>
<td>Receipt of curative treatment (ultrasound +/- AFP)</td>
<td>(24 observational studies)</td>
<td>Ⓞ⓷⓴  LOW</td>
<td>OR 2.19 (1.89 to 2.53)</td>
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</tbody>
</table>

*Upgraded because of large effect size
The “Birth Cohort” – The Present US Problem

- Born before 1945 (aged > 55 years at death)
- Born 1945-1965 (aged 35-68 years at death)
- Born 1966-1970 (aged 35-47 years at death)
HCC in the VA System: 2013

Incidences of HCC by underlying liver disease

Deaths in patients with HCC per 100,000 patient-years

Cases of HCC in VA System - 2013

Beste L et al. Gastroenterology 2015
Kaplan-Meier curves of survival free of HCC by cirrhosis and SVR status after DAA-only antiviral treatment:
SVR is associated with a reduction in HCC risk both among patients with cirrhosis and those without cirrhosis.

DAA-induced SVR is associated with a 71% reduction in HCC risk
Don’t Stop Surveillance Post-SVR in Patients with Advanced Fibrosis

• Natural history is evolving
• Many studies suggest that although liver stiffness may improve after SVR, cirrhosis and attendant HCC risk remains
• Probability of HCC seems to plateau in the second year following SVR (Kanwal et al. #0888)
• 1.6-fold increase in HCC incidence in the 7 year interval between 2001-2007 compared to 2008-2014 (Ioannou et al. #0274)
Once HCC is Successfully Treated, Don’t Forget to Treat HCV!

DAA group vs no DAA group
HR=0.39 (p=0.03)

**Landmark analysis of risk of HCC recurrence by DAA treatment status**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>DAA Untreated</th>
<th>DAA Treated</th>
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<tr>
<td>0</td>
<td>0.0</td>
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Number at risk
- DAA group: 102
- No DAA group: 102

Survival
- DAA group (solid blue line)
- No DAA group (dashed red line)

Risk of Recurrence
- DAA Untreated (blue line)
- DAA Treated (orange line)
296,707 NAFLD patients; 296,707 matched controls.

Over 2,382,289 PY of follow-up, 490 HCCs (0.21/1000 PY).

Incidence significant higher among NAFLD patients vs controls (0.02/1000 PY; HR 7.62; 95% CI 5.76–10.09).

Cirrhotics had the highest annual incidence of HCC (10.6/1000 PY, ranging 1.6 to 23.7 per 1000 PY).

Highest risk in older Hispanics with cirrhosis.

20% of NAFLD patients with HCC had no evidence of cirrhosis.

Absolute risk of HCC higher than accepted thresholds for most patients with NAFLD cirrhosis.

What About NAFLD?

Kanwal F, et al. Gastro 2018
How Do We Prioritize Those Most In Need?

• Can we develop more rational, “living models” of risk, to inform those most in need of surveillance?
• Prioritize resources
• Prioritize workflow
• Diminish psychological harm
## Final HCC Risk Models

<table>
<thead>
<tr>
<th>CIRRHOSIS + No SVR</th>
<th>CIRRHOSIS + SVR</th>
<th>No CIRRHOSIS + No SVR</th>
<th>No CIRRHOSIS + SVR</th>
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<tbody>
<tr>
<td>Age</td>
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<td>INR</td>
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* Available at [www.hccrisk.com](http://www.hccrisk.com)
Online HCC Risk Prediction
Web-based tool: www.hccrisk.com

| Cirrhosis | Yes | Yes | Yes | No | No | No |
| SVR       | No  | Yes | Yes | No | No | Yes |
| Age       | 65  | 55  | 66  | 65 | 55 | 65  |
| Albumin   | 3.3 | 4.1 | 3.6 | 3.8| 4.1| 4.1 |
| AST       | 40  | 25  | 45  | 35 | 35 | 35  |
| ALT       | 30  | 35  | 30  | 30 | 45 | 45  |
| Platelet  | 110 | 145 | 110 | 145| 201| 250 |
| 3-yr HCC risk | 25.9% | 1.6% | 11.1% | 7.0% | 0.6% | 0.3% |

**Screening “Recommended”**

**Screening Not “Recommended”**

Web Developer: Ted James, MD UNC

Courtesy of G. Ioannou #0094
Ioannou GN et al. J Hepatol 2018
CONCLUSIONS: HCC Risk Stratification

- HCV Antiviral Treatment
  Cirrhosis: Yes/No
  SVR: Yes/No

Baseline HCC Predictors

HCC RISK MODEL

- HIGH RISK >3% per yr
- MEDIUM RISK 1-3% per yr
- LOW RISK <1% per yr

- Screening?
- Outreach for screening?
- Clinical trials of screening/chemoprevention?
- Different screening strategies?

Courtesy of G. Ioannou #0094
Ioannou GN et al. J Hepatol 2018
Even Very High-risk Patients Rarely Receive Routine HCC Surveillance

Annual HCC Surveillance With Either US or AFP in Patients With HCV and Cirrhosis (n=9369)

- Routine: 12%
- Inconsistent: 58.5%
- None: 29.5%

Routine testing = tests done during at least 2 consecutive years in the 4 years after diagnosis of cirrhosis; inconsistent testing = ≥1 test during the same timeframe.

AFP = alpha-fetoprotein; US = ultrasound.
Utility of Surveillance

• Surveillance with ultrasound is cost effective (annual incidence $\geq 1\%$)
• Associated with early stage at diagnosis and improved survival
• *Utilization* and sensitivity of surveillance test have been modeled ($>32\%$ and 42\%, respectively)
Barriers to Surveillance

Underutilization

Provider
- Cirrhosis? Guidelines?
- Clinical concerns

System/Patient
- Availability
- Scheduling
- Patient f/u

Test
- Operator-dependence
  - Tech v. MD
  - Obesity

Footnotes

a. Multiphase CT or MRI in select patients
Some high-risk patients may undergo multiphase CT or MRI for HCC surveillance (depending on patient body habitus, visibility of liver at ultrasound, being on the transplant waiting list and other factors).

b. Noncategorizable
These are due to technical problem such as image omission or severe degradation
Summary

• HCC is a complex and heterogeneous cancer
• Diagnosing HCC at early stages requires identifying at-risk individuals and enrolling them in a surveillance program
• New tools can help us prioritize those at highest risk
• Implementation of surveillance programs has been challenging