Issues with Surveillance in NASH Population

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@docamitgs
“Globesity” and NASH – the future of HCC

Prevalence of obesity (%)*

- <5
- 5–14.9
- 15–24.9
- Data not available
- Not applicable

* BMI ≥ 30 kg/m²
NASH is increasingly common etiology for HCC

Consecutive patients referred to Newcastle-upon-Tyne Hospitals NHS Foundation Trust
NASH HCC incidence anticipated to increase worldwide

China largest increase (82%) while Japan smallest increase (44%)
Europe: France largest increase (117%); UK smallest increase (88%)
US increases by 122%
HCC surveillance is recommended by several professional society guidelines

Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma

Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma

Management of Hepatocellular Carcinoma (HCC)

U.S. Department of Veterans Affairs
Veterans Health Administration
VA Hepatitis C Resource Center Program &
VA National Clinical Public Health Program

UT Southwestern
Harold C. Simmons
Comprehensive Cancer Center
Level I data: HCC surveillance reduces mortality in patients with chronic hepatitis B

<table>
<thead>
<tr>
<th>Variable</th>
<th>Screen Group (n=9373)</th>
<th>Control Group (n=9443)</th>
</tr>
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<tbody>
<tr>
<td>HCC cases</td>
<td>86</td>
<td>67</td>
</tr>
<tr>
<td>% Stage I</td>
<td>60.5%</td>
<td>0%</td>
</tr>
<tr>
<td>% Curative treatment</td>
<td>46.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td># HCC death</td>
<td>32</td>
<td>54</td>
</tr>
<tr>
<td>Mortality (per 100,000)</td>
<td>83.2</td>
<td>131.5</td>
</tr>
<tr>
<td>Rate Ratio</td>
<td>0.63 (0.4-0.9)</td>
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Zhang et al. Cancer Res Oncol 2004
Results may not apply to population we see today in Western World, particularly those with NASH

Chinese screening population in 1990s

Western screening population now

Slide courtesy of Claude Sirlin
Level II data: HCC surveillance associated with improved survival in patients with cirrhosis

Singal et al PLOS Medicine 2014
Level II data: HCC surveillance associated with improved survival in patients with cirrhosis

Pooled Odds of 3-year Survival
I-squared= 81.6% (95%CI 73.3-87.3%)
Level II data: Recent study questioning benefits of HCC surveillance

N=238 cases and 238 controls
Improving access to surveillance and test effectiveness are crucial to optimizing benefits.
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The primary cohort at-risk for HCC are patients with cirrhosis.

- Nonalcoholic steatohepatitis
- Hepatitis B viral infection
- Alcoholic liver disease
- Hepatitis C viral infection
- Chronic hepatitis
- Cirrhosis
- Chronic inflammation
- HCC
Patients with NASH cirrhosis are sufficiently high risk for HCC surveillance to be cost-effective

Incidence: 0.6 (2001-2007) vs. 1.2 (2008-2014) per 100 patient-years

* NASH defined by cirrhosis + obesity/DM and exclusion of other etiologies (2001– 2014)
HCC surveillance is underused, particularly by non-gastroenterologists

Singal et al. J General Int Med 2012
Providers report potential barriers to HCC surveillance

<table>
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<tr>
<th>Provider-reported barriers</th>
<th>Safety-net health system (n=77)</th>
<th>Tertiary care system (n=100)</th>
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Under-recognition of cirrhosis more common in NASH patients than HCV cirrhosis

UTSW study found 38.8% of HCC patients had unrecognized cirrhosis at diagnosis. 9 of 11 (81.8%) NASH patients had unrecognized cirrhosis (OR 8.3).

National VA study with 1201 HCC patients found 24.6% had unrecognized cirrhosis. NAFLD (n=70) associated with unrecognized cirrhosis (OR 4.8, 95%CI 2.4 – 9.3).
Many NASH HCC patients do not have cirrhosis

Consecutive patients referred to Newcastle-upon-Tyne Hospitals NHS Foundation Trust (2000-2010)
Many NASH HCC patients do not have cirrhosis

Very high probability non-cirrhotic: Histology and no features on imaging
High probability non-cirrhotic: APRI <1; no features on imaging; NL albumin, plt, INR

### NASH HCC associated with absence of cirrhosis

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<th>Patients (n=1221)</th>
<th>aOR (95% CI)</th>
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<tr>
<td>Female sex</td>
<td>285</td>
<td>1.44 (1.01 – 2.05)</td>
</tr>
<tr>
<td>Age &lt; 63</td>
<td>585</td>
<td>1.05 (0.75- 1.45)</td>
</tr>
<tr>
<td>Etiology (ref: HBV)</td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis C</td>
<td>249</td>
<td>0.25 (0.13 – 0.48)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>349</td>
<td>0.56 (0.33 – 0.93)</td>
</tr>
<tr>
<td><strong>NAFLD</strong></td>
<td><strong>181</strong></td>
<td><strong>2.59 (1.58 – 4.26)</strong></td>
</tr>
<tr>
<td>Other</td>
<td>43</td>
<td>0.41 (0.14 – 1.24)</td>
</tr>
<tr>
<td>No risk factor</td>
<td>146</td>
<td>4.28 (2.58 – 7.10)</td>
</tr>
</tbody>
</table>

37% of NASH HCC patients did not have cirrhosis

Consecutive HCC patients from 5 Dutch academic centers
NASH patients without cirrhosis are low risk for HCC

1-, 3-, and 5-year cumulative incidences were 0.2%, 0.8%, 1.0%

Development of cirrhosis was not included as time-varying covariate

* NAFLD defined by ICD-9 code (571.8%) and exclusion of ICD-9 codes for other etiologies

Lee et al. Int J Cancer 2017
NASH patients without cirrhosis are low risk for HCC

N= 296,707 NAFLD

N= 4235 cirrhosis; 292,366 no cirrhosis

Incidence 0.02 per 100 patient-years

0.008 per 100 patient-years

* NAFLD defined by exclusion of other etiologies

Kanwal et al. Gastro 2018
Simple predictive model using age and ALT in non-cirrhotic NASH may stratify HCC risk

10-year cumulative incidence rates:

- 0.36 (0 – 1.08)
- 1.67 (0 – 3.63)
- 2.92 (1.07 – 4.77)
- 12.4 (5.99 – 18.8)
GRADE-based recommendations for surveillance in patients with NASH

1. NASH patients with cirrhosis should be screened for HCC according to established guidelines for patients with cirrhosis

2. The true incidence of HCC remains to be studied in NASH patients without cirrhosis, and systematic HCC screening cannot be recommended based on current data

3. Predictive models of HCC risk in NASH patients need to be developed
Improving access to surveillance and test effectiveness are crucial to optimizing benefits.
Sensitivity of ultrasound for early tumor detection varies substantially between centers

15 studies 1994 – 2016

Pooled

Sensitivity (95% CI)

< 50% sensitivity

> 50% sensitivity

0.21 (0.05 – 0.51)

0.33 (0.04 – 0.78)

0.33 (0.04 – 0.78)

0.67 (0.22 – 0.96)

0.82 (0.70 – 0.91)

0.25 (0.03 – 0.65)

0.24 (0.17 – 0.33)

0.44 (0.14 – 0.79)

0.36 (0.21 – 0.53)

0.68 (0.45 – 0.86)

0.65 (0.56 – 0.73)

0.32 (0.18 – 0.48)

0.56 (0.21 – 0.86)

0.89 (0.52 – 1.00)

0.26 (0.14 – 0.41)

0.47 (0.33 – 0.61)

Tzartzeva et al Gastroenterology 2018

Slide courtesy of Claude Sirlin
Nearly 1 in 5 ultrasounds are inadequate quality for HCC surveillance in patients with cirrhosis

- Retrospective cohort study of 941 patients undergoing surveillance US

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<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio (95% CI)</th>
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<tr>
<td><strong>Cirrhosis etiology</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Reference 2.02 (0.67 – 6.10)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1.84 (1.09 – 3.09)</td>
</tr>
<tr>
<td>Alcohol-related</td>
<td>1.84 (1.09 – 3.09)</td>
</tr>
<tr>
<td>NASH-related</td>
<td>2.48 (1.30 – 4.75)</td>
</tr>
<tr>
<td><strong>BMI category</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Reference 2.60 (1.36 – 4.97)</td>
</tr>
<tr>
<td>Obese</td>
<td>8.86 (4.02 – 19.5)</td>
</tr>
<tr>
<td>Morbidly obese</td>
<td></td>
</tr>
<tr>
<td><strong>Child Pugh B/C</strong></td>
<td>1.65 (1.06 – 2.57)</td>
</tr>
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Simmons et al. Aliment Pharm Ther 2017
Benefits are only half of the equation to determine screening program value.
Potential Physical Harms of HCC Surveillance

- Retrospective cohort of 680 cirrhosis patients over 3 years
- Surveillance detected 48 HCC (70% (n=34) early)
- Physical harms observed in 187 (28%)
- Moderate-severe harm in 59 (10%) patients
- AFP-related harm associated with viral etiology (OR 5.3), whereas ultrasound-related harm was associated with non-viral etiology (OR 1.6)
Summary

◆ The incidence of NASH HCC is rapidly rising

◆ Patients with NASH cirrhosis have sufficient HCC risk and should undergo routine surveillance
  - Biomarkers may help improve patient recognition

◆ Patients with non-cirrhotic NASH do NOT have sufficient HCC risk
  - Predictive models may help identify at-risk subgroup

◆ Ultrasound may be less effective (lower sensitivity AND lower specificity) in patients with NASH
  - Blood-based surveillance biomarkers needed