MASLD-related Hepatocellular Carcinoma: Controversies and Challenges

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Learning Objectives:

• Understand challenges applying the new nomenclature for steatotic liver disease.
• Understand patient characteristics that increase risk for HCC
• Describe individualized approaches to screening and challenges with screening.
Primary liver cancer is the 7th most frequently occurring cancer worldwide, but is the 2nd most common cause of cancer mortality.
Between 41,000-42,000 individuals are diagnosed each year with cancer of the liver or intrahepatic bile ducts. 80% have HCC

### Estimated New Cases in 2023
- **41,210**

### % of All New Cancer Cases
- **2.1%**

### Estimated Deaths in 2023
- **29,380**

### % of All Cancer Deaths
- **4.8%**

### 5-Year Relative Survival
- **21.6%**
  - **2013-2019**

New cases come from SEER 12. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Trend Analysis Software.
The 2020 incidence rate is displayed but not used in the fit of the trend line(s). Impact of COVID on SEER Cancer Incidence 2020 data

New cases are also referred to as incident cases in other publications. Rates of new cases are also referred to as incidence rates.
Racial and Ethnic Disparities in HCC Incidence

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian/Alaskan Native</td>
<td>11.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9.8</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>9.1</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>8.1</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>4.6</td>
</tr>
</tbody>
</table>


Mortality Related to Liver Cancer is Increasing.

Liver Cancer Incidence is Decreasing.

The Etiology of Liver Disease leading to HCC has Changed

Figure 1. Prevalence of HCC in waitlisted candidates by etiology relative to that in 2002. Dotted lines represent linear trends.

Case Presentation

• 67 year-old man was referred for a liver mass.
  • Unaware that he had liver disease

• He has had chronic GI upset but recently has severe abdominal pain whenever he eats.

• Ultrasound revealed a large heterogeneous liver with an ill-defined focal hypoechoic area in the right hepatic lobe (3.4 x 3.1 x 3.7 cm). The liver demonstrates cirrhotic morphology.

• MRI demonstrated a large mass with arterial hyperenhancement and corresponding washout.
Case Presentation

• Previously unaware that he had liver disease
  • Drinks 11 alcoholic drinks/week.

• Past Medical History:
  • Hyperlipidemia
  • Hypertension
  • Obesity
  • Prostate cancer

• Physical Exam:
  • Well-appearing with normal vital signs
  • BMI 34.9
  • Oriented to person, place and time
  • Anicteric sclera
  • Bronze skin, acanthosis nigricans
  • Mild tenderness to palpation
  • No dullness to percussion
  • No peripheral edema
• The mass was infiltrative and tumor involved segments 5, 6, 7 and 8 and partly into IVb. Largest diameter 13 cm.

• There is tumor thrombus extending into the right and main portal veins.

• There are minute lesions in the left hepatic lobe worrisome for metastatic HCC.
## Diagnostic Criteria for MASLD

### *Cardiometabolic criteria*

#### Adult Criteria

- At least 1 out of 5:
  - BMI ≥ 25 kg/m² [23 Asia] OR WC > 94 cm (M) 80 cm (F) OR ethnicity adjusted equivalent
  - Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] OR 2-hour post-load glucose levels ≥ 7.8 mmol/L
    - [≥140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/L] OR type 2 diabetes OR treatment for type 2 diabetes
  - Blood pressure ≥ 130/85 mmHg OR specific antihypertensive drug treatment
  - Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] OR lipid lowering treatment
  - Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) OR lipid lowering treatment

#### Pediatric Criteria

- At least 1 out of 5:
  - BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] OR WC > 95th percentile OR ethnicity adjusted equivalent
  - Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] OR serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] OR 2-hour post-load glucose levels ≥ 7.8 mmol
    - [140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes
  - Blood pressure age < 13y, BP ≥ 95th percentile OR ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg OR specific antihypertensive drug treatment
  - Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] OR lipid lowering treatment
  - Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] OR lipid lowering treatment

https://www.aasld.org/new-masld-nomenclature
Decision Support Tool

https://www.aasld.org/new-masld-nomenclature
Steatotic Liver Disease (SLD)

MASLD and increased alcohol intake* (MetALD)

MASLD predominant ALD predominant

Weekly alcohol intake (g)
140/210 210 280 350/420

Average daily alcohol intake (g)
20/30 30 40 50/60

*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)

**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism

***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

https://www.aasld.org/new-masld-nomenclature
Obesity and Cancer Risk:

![Graph showing the relative risk of death associated with obesity across different types of cancer.](image)


El-Serag HB, Rudolph KL. Gastroenterology. 2007;132(7):2557-76
Diabetes and Hepatocellular Carcinoma:

Figure 8. Diabetes and the risk of HCC. The study examined 173,463 patients with diabetes and 650,620 without diabetes. No patient had acute or chronic liver disease recorded before, during, or within 1 year of his or her index hospitalization. Reprinted with permission.8
Figure 2
Proportion of hepatocellular carcinoma secondary to non-alcoholic fatty liver disease worldwide, by WHO region

How does NAFLD-related HCC differ from non-NAFLD HCC?

• In 61 studies (1980-2021) of 94,636 patients with HCC, NAFLD accounted for 15.1% of HCC.

• Compared to non-NAFLD HCC patients, NAFLD-HCC patients
  • were older, had higher BMI and more likely to have metabolic comorbidities, e.g. diabetes, HTN, HLD) or cardiovascular disease at presentation.
  • were more likely to be non-cirrhotic 38.5% (95% CI 27.9-50.2), compared to 14.6% in non-NAFLD HCC (95% CI 8.7-23.4)
  • were less likely to have received surveillance 32.8% (95%CI 12-63.7), compared to 55.7% (95% CI 24-83)
  • had larger tumors
  • had similar BCLC, ECOG, AFP, treatment allocation and survival.
  • less likely to undergo transplant in favor of resection.

The prevalence of NAFLD has doubled over the past two decades and is approximately 30%.

20% of patients with NAFLD-related HCC did not have cirrhosis

- Retrospective cohort study of 296,707 NAFLD patients in the VA.
- The absolute risk of HCC in NAFLD is low 0.21/1000 person-years or 0.8% five-year and 1.7% ten-year cumulative HCC risk.
- The absolute risk is too low in non-cirrhotic patients to recommend HCC surveillance.

Risk was highest among oldest Hispanics.

Kanwal et al. Gastroenterology 2018; 155: 1828-1837
In 18 studies of 470,404 patients with NAFLD.
  • Almost half from the VA study.

Pooled incidence rate 2.39/100 person years (95% CI 1.4-4.08)
  • Cirrhosis: 3.78/100 person years
  • Cirrhosis enrolled in screening: 4.62/100 person years
  • Non-cirrhotic NAFLD: 0.03/100 person years

Alcohol use interacts with cardiometabolic risk factors and impacts risk of decompensation.
Cirrhosis is the Strongest Risk Factor for HCC

- 85-95% of patients with HCC have cirrhosis.¹

- The risk of developing HCC ranges from 1-8% each year.²

- Rarely develops in patients under age 40

- Male predominance with 2:1 to 4:1 male:female ratio.
  - Men develop HCC 5 years earlier than women

- The 5-year cumulative risk for development of HCC in patients with cirrhosis ranges from 5-30% and depends on etiology of liver disease, region, ethnicity, and stage of cirrhosis.³
  - The highest risk of HCC is among patients with decompensated cirrhosis.

Risk and Surveillance:

Only between 6% and 25% of HCC patients received HCC screening. Consistent surveillance leads to earlier diagnosis and improved survival.

- **Recommended Screening Modality: Ultrasound ± α-fetoprotein (AFP)**
  - Ultrasound alone: Sensitivity 58-89%, Specificity 90%; operator-dependent and may be inadequate in up to 20%.
  - Neither CT nor MRI are *cost-effective* for surveillance and have increased risk of false-positives
  - Patient characteristics (e.g. ascites, obesity) limit sensitivity of ultrasound

- **Recommended Screening Interval**: 6 months
## Performance of Imaging Studies

### Table 1. Test Performance of Imaging Modalities for HCC

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Unit of Analysis</th>
<th>Sensitivity (95% CI)</th>
<th>Studies, n</th>
<th>Specificity (95% CI)</th>
<th>Studies, n</th>
<th>Positive LR</th>
<th>Negative LR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Detection of HCC</strong></td>
<td></td>
<td></td>
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<tr>
<td>Surveillance settings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US without contrast</td>
<td>Patient</td>
<td>0.78 (0.60-0.89)</td>
<td>4</td>
<td>0.89 (0.80-0.94)</td>
<td>3</td>
<td>6.8 (4.2-11)</td>
<td>0.25 (0.13-0.46)</td>
</tr>
<tr>
<td>CT</td>
<td>Patient</td>
<td>0.84 (0.59-0.95)</td>
<td>2</td>
<td>0.99 (0.86-0.999)</td>
<td>2</td>
<td>60 (5.9-622)</td>
<td>0.16 (0.06-0.47)</td>
</tr>
<tr>
<td>US without contrast</td>
<td>Lesion</td>
<td>0.60 (0.24-0.87)</td>
<td>1</td>
<td>No data</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CT</td>
<td>Lesion</td>
<td>0.62 (0.46-0.76)</td>
<td>1</td>
<td>Insufficient data</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Non-surveillance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US without contrast</td>
<td>Patient</td>
<td>0.73 (0.46-0.90)</td>
<td>8</td>
<td>0.93 (0.85-0.97)</td>
<td>6</td>
<td>11 (5.4-21)</td>
<td>0.29 (0.13-0.65)</td>
</tr>
<tr>
<td>CT</td>
<td>Patient</td>
<td>0.83 (0.76-0.88)</td>
<td>17</td>
<td>0.91 (0.84-0.95)</td>
<td>12</td>
<td>9.1 (5.1-16)</td>
<td>0.19 (0.13-0.27)</td>
</tr>
<tr>
<td>MRI</td>
<td>Patient</td>
<td>0.86 (0.79-0.91)</td>
<td>14</td>
<td>0.89 (0.82-0.93)</td>
<td>12</td>
<td>7.7 (4.6-13)</td>
<td>0.16 (0.10-0.24)</td>
</tr>
<tr>
<td>US without contrast</td>
<td>Lesion</td>
<td>0.59 (0.42-0.74)</td>
<td>11</td>
<td>0.83 (0.53-0.95)</td>
<td>2</td>
<td>3.4 (1.2-9.4)</td>
<td>0.50 (0.37-0.66)</td>
</tr>
<tr>
<td>US with contrast</td>
<td>Lesion</td>
<td>0.75 (0.57-0.88)</td>
<td>9</td>
<td>0.97 (0.84-0.999)</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CT</td>
<td>Lesion</td>
<td>0.76 (0.72-0.80)</td>
<td>80</td>
<td>0.89 (0.84-0.93)</td>
<td>21</td>
<td>7.1 (4.7-11)</td>
<td>0.26 (0.22-0.32)</td>
</tr>
<tr>
<td>MRI</td>
<td>Lesion</td>
<td>0.83 (0.80-0.86)</td>
<td>82</td>
<td>0.87 (0.79-0.93)</td>
<td>20</td>
<td>6.5 (3.8-11)</td>
<td>0.20 (0.16-0.24)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluation of focal liver lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>US without contrast</td>
</tr>
<tr>
<td>US with contrast</td>
</tr>
<tr>
<td>CT</td>
</tr>
<tr>
<td>MRI</td>
</tr>
<tr>
<td>US without contrast</td>
</tr>
<tr>
<td>US with contrast</td>
</tr>
<tr>
<td>CT</td>
</tr>
<tr>
<td>MRI</td>
</tr>
</tbody>
</table>

CT = computed tomography; HCC = hepatocellular carcinoma; LR = likelihood ratio; MRI = magnetic resonance imaging; US = ultrasonography.

Screening, specifically CT and MRI may be associated with **potential harm**, caused by false positives.
# Blood-Based Biomarkers for HCC

## Table 2: Status of surveillance tests for the early detection of hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Test</th>
<th>Early detection research network (EDRN) phase of validation</th>
<th>Performance characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>US plus AFP[55]</td>
<td>5</td>
<td>Sensitivity 61% Specificity 92%</td>
</tr>
<tr>
<td>AFP-L3%[69]</td>
<td>3</td>
<td>Sensitivity 62% Specificity 90%</td>
</tr>
<tr>
<td>DCP[69]</td>
<td>3</td>
<td>Sensitivity 40% Specificity 81%</td>
</tr>
<tr>
<td>Multitarget algorithm[70]</td>
<td>2</td>
<td>Sensitivity 82% Specificity 87%</td>
</tr>
<tr>
<td>GALAD[71]</td>
<td>2/3</td>
<td>Sensitivity 54–72% Specificity 90%</td>
</tr>
<tr>
<td>Doylestown plus[72]</td>
<td>2/3</td>
<td>Sensitivity 90% Specificity 95%</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha fetoprotein; AFP-L3%, *Lens culinaris* lectin binding subfraction of AFP; DCP, des-gamma carboxyprothrombin; GALAD, gender, age, AFP-L3%, AFP, and DCP model; US, ultrasound.
Disparities in HCC Screening

Potential patient-, provider-, and health care system-specific barriers that contribute to disparities in HCC surveillance

HCC Screening rates are generally lower in Black individuals, those who are uninsured, those who live in neighborhoods with higher levels of poverty.

Another barrier to screening and early diagnosis is limited availability of high-quality ultrasound. Ultrasound visualization score is rarely reported.
LI-RADS 5 Lesions

- Enhance
- Washout
- Threshold growth
- Enhancing capsule

Diagnosis:

Name: ____________________________ Age: ______

Doctor’s name: ____________________

Liver cancer
Take Home Points

• The burden of steatotic liver disease-related HCC is increasing.

• All patients with cirrhosis should be screened for HCC every six months. There is limited data about other populations.

• Ultrasound ± AFP is the recommended screening modality.
  • Some patient characteristics may require cross-sectional imaging.

• A team-based multidisciplinary approach to HCC management is standard of care.
  • Treatment must be individualized based on tumor burden, performance status and liver function.

• The treatment landscape has changed dramatically since 2017 and there are new treatments on the horizon.
Thank You

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References

References


