The Latest in Managing Hepatocellular Carcinoma (HCC)

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Disclosures

- Bayer Pharmaceuticals: Research Support (to institution)
- Inovio Pharmaceuticals: Research Support (to institution)
- Gilead Pharmaceuticals: Research Support (to institution)
- Ad board: Exelixis
Introduction

- Liver cancer – dreaded complication of cirrhosis
- 3rd leading cause of cancer death worldwide
- Common cause of death among cirrhotic patients
- Incidence 1-2% per year
- Risk not eliminated with cure/control of underlying cirrhosis (EtOH, HCV, HBV)
  - Accumulated mutations in cirrhotic nodules
  - Telomere shortening
- Incidence $\approx$ Mortality
Outline

- Primary prevention – Abstracts 91, 93, 2378
- HCC Risk Assessment – Abstracts 17, 94, 213
- Updates to UNOS Exception Points – Abstracts 163, 95, 92
- Update in HCC therapy – Abstracts 270, 275, LB-2, ESMO
  - 1\textsuperscript{st} line approved
  - 2\textsuperscript{nd} line approved options
  - What to expect in 2019
Outline

- Primary prevention
- HCC Risk Assessment
- Updates to UNOS Exception Points
- Update in HCC therapy
  - 1\textsuperscript{st} line approved
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  - What to expect in 2019
Primary prevention
- Can liver cancer be prevented at the population health level?
Aspirin use and the risk of HCC

- Two cohorts
  - NHS (N=87,507, ♂️)
  - HPFS (N=48,864, ♂️)
- 26+ years of follow-up
- ASA self-report
  - 81mg/d or 325mg twice weekly → exposed

- HR 0.51, 95% CI 0.34-0.77

* Model conditioned on age (years), sex/cohort, race/ethnicity, type 2 diabetes, hypertension, hyperlipidemia, statin use, metformin use, and non-aspirin nonsteroidal anti-inflammatory drug (NSAID) use, with all covariates updated over time.
Lipophilic statins and the risk of HCC

- **Swedish population database**
  - cHBV N = 3,906
  - cHCV N = 12,762
- **Median f/u 8 years**
- **Lower HCC risk seen with lipophilic statins (simvastatin, lovastatin, atorvastatin)**

Cumulative incidence of HCC with lipophilic statins (A) or hydrophilic statins (B)

Cumulative defined daily dose (cDDD) of lipophilic statins and risk for HCC:

<table>
<thead>
<tr>
<th>No. Cases / Person-Years</th>
<th>Non-use</th>
<th>30-299 cDDD</th>
<th>300-599 cDDD</th>
<th>≥ 600 cDDD</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>1 (Reference)</td>
<td>0.81 (0.49-1.14)</td>
<td>0.59 (0.48-0.82)</td>
<td>0.43 (0.29-0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1 (Reference)</td>
<td>0.85 (0.51-1.22)</td>
<td>0.57 (0.47-0.79)</td>
<td>0.46 (0.31-0.72)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Model adjusted for age (years), sex, duration of HBV/HCV (years), cirrhosis (yes vs no), ever-use of antiviral therapy, type 2 diabetes (yes vs no), obesity (yes vs no), use of aspirin (yes vs no), use of metformin (yes vs no).
Secondary prevention
- Can liver cancer be prevented in at-risk population?
Statin exposure associated with improved survival in new initiators (propensity-matched, risk-set matched)

Non-time updating: HR 0.79
Unadjusted HR 0.40 (95%CI 0.37-0.43)

<table>
<thead>
<tr>
<th></th>
<th>Time-Updating Exposure</th>
<th>Per Year, Time-Updating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>All</td>
<td>0.39 (0.36-0.44)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CTP A</td>
<td>0.40 (0.36-0.44)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CTP B</td>
<td>0.43 (0.35-0.51)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CTP C</td>
<td>0.58 (0.29-1.14)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>EtOH</td>
<td>0.40 (0.35-0.46)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HCV</td>
<td>0.48 (0.36-0.65)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HCV+ETOH</td>
<td>0.52 (0.42-0.64)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>NASH</td>
<td>0.38 (0.32-0.45)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Other</td>
<td>0.31 (0.22-0.44)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Models adjusted for age, gender, BMI, Child-Turcotte-Pugh, tobacco use, cirrhosis comorbidity, platelet count, AST, ALT, diabetes, HTN, CAD, facility factors, substance abuse, AUDIT-C, duration of prior statin exposure, niacin exposure, fibrate exposure, HCV DAA, HBV DAA, LDL, TGL and HDL. IPTW weighting used to generate marginal structural models to adjust for interaction of statin use and cholesterol values.
Statin exposure associated with reduced HCC and decompensation, but not reduced MACE in new initiators

Models adjusted for age, gender, BMI, Child-Turcotte-Pugh, tobacco use, cirrhosis comorbidity, platelet count, AST, ALT, diabetes, HTN, CAD, facility factors, substance abuse, AUDIT-C, duration of prior statin exposure, niacin exposure, fibrate exposure, HCV DAA, HBV DAA, LDL, TGL and HDL. IPTW weighting used to generate marginal structural models to adjust for interaction of statin use and cholesterol values.
Lipophilicity and Dose

Kaplan DE, et al. Unpublished
Primary chemoprevention – Take home

- No signal that ASA or statins harmful with regard to liver outcomes

- Major issues with *confounding by indication*
  - Assignment to treatment not random, more likely for low-risk individuals to be exposed
  - Evidence not strong enough to recommend blanket utilization

- Do ASA or statins prevent cancer by preventing fibrosis/cirrhosis?
  - Statins do appear to reduce progression of disease in patients with cirrhosis
Outline

- Primary prevention
- HCC Risk Assessment
- Updates to UNOS Exception Points
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  - What to expect in 2019
HCC Surveillance / Risk Prediction

- **AASLD recommends surveillance for hepatocellular carcinoma**
  - Patients with cirrhosis
  - Patients with chronic HBV and certain high risk features
    - Family history
    - Age
    - Area of birth

- **Antiviral therapy modifies this risk**
  - SVR12 in HCV – 75-80% risk reduction
  - HBV DAA therapy – benefit less well defined, but > 5 years therapy ↓

- **Do all patients have enough risk to screen? How to choose?**
HCC Risk Prediction Models

- Most HCV-infected patients undergo antiviral treatment
- >95% will achieve SVR
- SVR reduces the risk of HCC (75-80%)
- Substantial HCC risk remains after SVR in patients with pre-existing cirrhosis (from <0.5% to >5% per year depending on co-factors)
- Uncertainties:
  - What is the residual HCC risk?
  - Who to commit to surveillance?
  - How to do surveillance?
  - How long to continue?
  - Is one-size-fits all strategy to surveillance appropriate?
Concept: HCC Risk Stratification

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

Baseline HCC Predictors → HCC RISK MODEL → HCC RISK

- 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?
Started HCV antiviral therapy
2009-2015
N=45,810

IFN-only
N=10,332
23%

DAA+IFN
N=6179
13%

DAA-only
N=29,309
64%

Followed until 6/15/2017 for HCC Development
Range of follow-up = 1.5 to 8 yrs
Mean follow-up = 3.1 years
Incident HCCs = 1297 (0.9 cases per 100 person years)
HCC Risk Prediction Models

- Cirrhosis
  - SVR
  - No SVR
- No Cirrhosis
  - SVR
  - No SVR

Graph: Probability free from HCC diagnosis over years after start of HCV treatment.

Legend:
- Green: Cirrhosis with no SVR
- Orange: Cirrhosis with SVR
- Blue: No cirrhosis with no SVR
- Red: No cirrhosis with SVR
# Final HCC Risk Models

![HCC risk estimator](image)

### Hepatocellular Carcinoma (HCC) Risk Estimator

- **Purpose**: To estimate the 3-year risk of HCC in patients with hepatitis C virus (HCV) infection who have undergone antiviral treatment or in patients with cirrhosis caused by alcohol-related liver disease (ALD) or non-alcoholic fatty liver disease (NAFLD).
- **Data Entry**: Enter the patient's age and labs, using values obtained before the initiation of HCV treatment.
- **Risk Estimate**: Enter the patient's age and labs, using values obtained before the initiation of HCV treatment.
- **Risk Validation**: This risk estimator should not be used in patients with previously diagnosed HCC, prior liver transplant, or cirrhosis from other etiologies (e.g., alcoholic liver disease, non-alcoholic fatty liver disease, hepatitis B).
- **Risk Validation**: This risk estimator has not been validated among patients without prior HCV treatment.
- **Risk Validation**: This tool is not designed for use by patients.
- **Risk Validation**: For patients with Child A or B cirrhosis or Child C cirrhosis on the transplant waiting list, it is recommended they receive screening with abdominal ultrasound with or without serum AFP every 6 months.
- **Risk Validation**: Diagnostic evaluation for HCC among patients with abnormal screening results should include either multiphase CT or MRI.
- **Risk Validation**: Patients with confirmed HCC who wish to undergo treatment should be referred to a medical center with expertise in treating HCC and liver transplantation capabilities.

* Available at [www.hccrisk.com](http://www.hccrisk.com)

HCC Risk Prediction Models – Calibration/Discrimination

a. Cirrhosis and no SVR

Predicted vs observed survival free of HCC diagnosis for cirrhotics who did not achieve SVR

Cirrhosis + No SVR

Validation 0.70

Derivation 0.70

c. No cirrhosis and no SVR

Predicted vs observed survival free of HCC diagnosis for non-cirrhotics who did not achieve SVR

No Cirrhosis + No SVR

Validation 0.74

Derivation 0.75

b. Cirrhosis and SVR

Predicted vs observed survival free of HCC diagnosis for cirrhotics who achieved SVR

Cirrhosis + SVR

Validation 0.70

Derivation 0.70

d. No cirrhosis and SVR

Predicted vs observed survival free of HCC diagnosis for non-cirrhotics who achieved SVR

No Cirrhosis + SVR

Validation 0.77

Derivation 0.77

Greater net benefit for HCC screening based on risk models than for screen-all
HCC Risk Prediction Models in HCV - Conclusion

- Simple online predictor of individual’s HCC Risk using
  - Cirrhosis status
  - SVR status
  - Routinely available characteristics and labs
  - www.hccrisk.com

- Risk-based screening has greater net-benefit when modeled relative screen all approaches

- Can be used in shared decision-making with patients
Risk prediction of HCC in cHBV in DAA

- PAGE-B cohort
- HCC risk ≥ 5 years on DAA
- 2.3% developed HCC after 5 years of follow-up
- Only predictors of HCC
  - Baseline cirrhosis
  - Age > 50
- Reversion of fibrosis NOT protective
Risk prediction of HCC in cHBV after HBsAg seroclearance

High PAGE-B was associated with HCC after HBsAg seroclearance

<table>
<thead>
<tr>
<th>Year</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 5</td>
<td>0%</td>
<td>0%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Year 10</td>
<td>0%</td>
<td>1.9%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Year 15</td>
<td>0%</td>
<td>1.9%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Annual</td>
<td>0%</td>
<td>0.08%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Log-rank test

- High vs Intermediate: 0.009
- High vs Low: 0.009
- Low vs Intermediate: 0.421

Cumulative rates of HCC incidence

- High risk (N=242)
- Intermediate risk (N=164)
- Low risk (N=144)

Variable | No. Pts N=550 | HCC Cases N=14 | Total Pt-Years | Incidence Rate Per 1000 PY | *Multivariate Adjusted HR (95% CI) | P     |
<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PAGE-B (High Risk)</td>
<td>242</td>
<td>13</td>
<td>1795.4</td>
<td>7.2</td>
<td>11.8 (1.53–90.5)</td>
<td>0.018</td>
</tr>
<tr>
<td>Pre-Existing Cirrhosis Before HBsAg Seroclearance</td>
<td>87</td>
<td>10</td>
<td>675.5</td>
<td>14.8</td>
<td>9.62 (3.00–30.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
HCC Risk Prediction

- Liver cancer risk is not eliminated with virological control
  - Cirrhosis
  - Age

- Not associated with reduced risk (HBV):
  - Fibrosis regression
  - HBsAg loss

- For HCV, new risk prediction tool might improve selection for continued HCC surveillance
Outline

• Primary prevention

• HCC Risk Assessment

• Updates to UNOS Exception Points

• Update in HCC therapy
  • 1st line approved
  • 2nd line approved options
  • What to expect in 2019
# UCSF Downstaging Protocol

## Table 1. UCSF Downstaging Protocol

### Inclusion criteria

- **HCC exceeding UNOS T2 criteria, but meeting one of the following criteria:**
  1. Single lesion ≤8 cm
  2. 2 or 3 lesions each ≤5 cm with the sum of the maximal tumor diameters ≤8 cm
  3. 4 or 5 lesions each ≤3 cm with the sum of the maximal tumor diameters ≤8 cm

### Absence of vascular invasion based on cross-sectional imaging

### Criteria for successful downstaging

1. Residual tumor(s) within UNOS T2 criteria for deceased donor LT and to within UCSF criteria for live donor LT*
2. In patients with 4 or 5 tumors, successful downstaging requires obliteration (complete necrosis) of at least 1-2 tumor(s)

### Criteria for downstaging failure and exclusion from LT

1. Progression of tumor(s) to beyond inclusion criteria for downstaging based on tumor size and number
2. Invasion of a major hepatic vessel based on cross-sectional imaging or Doppler ultrasonography of the abdomen
3. Lymph node involvement by tumor or extrahepatic spread of tumor

### Additional guidelines

1. A minimal observation period of 3 months between downstaging and LT is required.
2. A patient with acute hepatic decompensation after downstaging treatment is not eligible for LT unless criteria for successful downstaging and minimal observation period are met.

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*UCSF criteria: 1 lesion ≤6.5 cm, 2-3 lesions each ≤4.5 cm with the sum of the maximal tumor diameters ≤8 cm.
UCSF Downstaging Protocol

- 65% success in achieving successful downstaging
  **Caveats:** ~25% of patients in the study had HBV and ~40% of patients treated with multi-modality LRT

Yao FY Hepatology 2015;61:1968-77
UNOS Downstaging Policy

❖ Standard Candidates
  • Single tumor <5cm
  • ≤ 3 tumors each < 3cm
  • AFP < 500 after LRT if AFP > 1000

❖ Downstage Candidates
  • Single tumor >5cm and ≤8cm
  • ≤ 3 tumors each < 5cm, TTD ≤ 8cm
  • ≤ 5 tumors each < 3cm, TTD ≤ 8cm
  • Successfully downstaged into T2 with LRT (imaging at least 4 weeks after LRT), 3 months stability
  • AFP < 500 after LRT if AFP > 1000

❖ 6 month delay, then MELD 28
❖ Standard 3 month elevations
❖ MELD capped at 34
❖ National Liver Review Board
Downstaging in practice

**MILAN**
- 1 lesion ≤ 5 cm
- Up to 3 lesions ≤ 3 cm
- No extra-hepatic disease or vascular invasion

N=3,276 (86%)
Total tumor diameter: 2.8 cm (2.3-3.7)

**“UNOS-DS”**
- 1 lesion 5.1-8 cm
- 2 or 3 lesions ≤ 5 cm
- 4 or 5 lesions ≤ 3 cm
- Total diameter ≤ 8 cm
- No extra-hepatic disease or vascular invasion

N=422 (11%)
Total tumor diameter: 5.8 cm (5.3-6.5)

**“AC-DS”**
- Tumor size, number or total tumor diameter beyond UCSF downstaging criteria
- No extra-hepatic disease or vascular invasion

N=121 (3.2%)
Total tumor diameter: 9.3 cm (8.5-10.6)

LVI: 14% 17% 24%
Understaged: 14% 33% 41%

Mehta N, AASLD 2018 #163
Downstaging in practice

Worse if AFP $\geq 100$
Worse if short wait time
### Adult Standard Exception Points

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Current Exception Points Assignment</th>
<th>Approved Exception Points Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholangiocarcinoma</td>
<td>MELD 22 (w/ 10% point escalator)</td>
<td>MMaT – 3 for DSA</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>MELD 22 (w/ 10% point escalator)</td>
<td>MMaT – 3 for DSA</td>
</tr>
<tr>
<td>Familial amyloid polyneuropathy</td>
<td>MELD 22 (w/ 10% point escalator)</td>
<td>MMaT – 3 for DSA</td>
</tr>
<tr>
<td>Hepatic artery thrombosis</td>
<td>MELD 40</td>
<td>MELD 40 for DSA</td>
</tr>
<tr>
<td>Hepatopulmonary syndrome</td>
<td>MELD 22 (w/ 10% point escalator if PaO\textsubscript{2} remains under 60 mmHg)</td>
<td>MMaT – 3 for DSA</td>
</tr>
<tr>
<td>Portopulmonary hypertension</td>
<td>MELD 22 (w/ 10% point escalator if repeat heart cath shows MPAP &lt;35)</td>
<td>MMaT – 3 for DSA</td>
</tr>
<tr>
<td>Primary Hyperoxaluria</td>
<td>MELD 28 (w/ 10% point escalator)</td>
<td>MMaT for DSA</td>
</tr>
<tr>
<td>HCC</td>
<td>Delay 6 months, then 28, 30, 32, 34</td>
<td>MMaT - 3 for DSA (after delay)</td>
</tr>
</tbody>
</table>

MMaT = Median MELD at Transplant
Removal of the HCC ladder

- Expect patients with HCC to experience longer wait times
- Higher wait-list drop out due to progression

**Approaches:**
- Resection with salvage OLT
- DAAs for HCC patients
- LDLT
- Bridging systemic therapy
Advantage of salvage liver transplantation

- Systemic review and meta-analysis to assess the short-term outcomes, overall survival (OS), and disease-free survival (DFS) between SLT and PLT for patients with HCC
- Fixed effects model and random effects model
- SLT had superior 1-year, 3-year, and 5-year OS and DFS compared with that of PLT.


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**Figure 5.** Overall survival outcomes between SLT group and PLT group: (A) 1-year, (B) 3-year, (C) 5-year.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odd ratio</th>
<th>Odd ratio M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adami 2003</td>
<td>7</td>
<td>17</td>
<td>319</td>
<td>195</td>
<td></td>
<td>0.06</td>
<td>[0.13, 0.22]</td>
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<tr>
<td>Beitzel 2001</td>
<td>10</td>
<td>18</td>
<td>37</td>
<td>70</td>
<td></td>
<td>1.11</td>
<td>[0.39, 3.16]</td>
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<tr>
<td>Bhatnagar 2014</td>
<td>10</td>
<td>31</td>
<td>135</td>
<td>340</td>
<td></td>
<td>0.23</td>
<td>[0.01, 1.58]</td>
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<tr>
<td>Chen 2005</td>
<td>13</td>
<td>18</td>
<td>101</td>
<td>136</td>
<td></td>
<td>0.06</td>
<td>[0.29, 1.2]</td>
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<tr>
<td>Del Gaudio 2008</td>
<td>10</td>
<td>16</td>
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<td>147</td>
<td></td>
<td>0.62</td>
<td>[0.21, 1.91]</td>
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<tr>
<td>Fantoni 2008</td>
<td>5</td>
<td>5</td>
<td>19</td>
<td>32</td>
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<td>Re 2012</td>
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<td>888</td>
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<td>640</td>
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<td>[0.77, 1.02]</td>
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<td>Wu 2012</td>
<td>3</td>
<td>10</td>
<td>144</td>
<td>200</td>
<td></td>
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<td>[0.01, 1.59]</td>
</tr>
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<td>Lin 2012</td>
<td>6</td>
<td>29</td>
<td>130</td>
<td>180</td>
<td></td>
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<td>[0.29, 1.27]</td>
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<tr>
<td>Margin 2005</td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>36</td>
<td></td>
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<td>[0.87, 1.5]</td>
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<tr>
<td>Ma 2012</td>
<td>9</td>
<td>17</td>
<td>131</td>
<td>169</td>
<td></td>
<td>0.37</td>
<td>[0.13, 1.05]</td>
</tr>
<tr>
<td>Sapidson 2010</td>
<td>9</td>
<td>17</td>
<td>32</td>
<td>34</td>
<td></td>
<td>0.61</td>
<td>[0.01, 1.4]</td>
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<tr>
<td>Scott 2009</td>
<td>10</td>
<td>20</td>
<td>40</td>
<td>73</td>
<td></td>
<td>1.31</td>
<td>[0.02, 1.09]</td>
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<tr>
<td>Shao 2017</td>
<td>11</td>
<td>28</td>
<td>125</td>
<td>217</td>
<td></td>
<td>0.42</td>
<td>[0.17, 1.05]</td>
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<tr>
<td>Tanaka 2015</td>
<td>15</td>
<td>17</td>
<td>122</td>
<td>77</td>
<td></td>
<td>0.95</td>
<td>[0.34, 2.85]</td>
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<td>Wang 2006</td>
<td>25</td>
<td>35</td>
<td>111</td>
<td>131</td>
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<td>1.07</td>
<td>[0.64, 1.77]</td>
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<tr>
<td>Wei 2012</td>
<td>25</td>
<td>35</td>
<td>111</td>
<td>147</td>
<td></td>
<td>0.74</td>
<td>[0.33, 1.64]</td>
</tr>
</tbody>
</table>

Total (95% CI): 1276

Heterogeneity: Chi² = 138.33, df = 17 (P < 0.001), I² = 76%
Test for overall effect: Z = 3.51 (P = 0.0009)
Direct Antiviral Agents after Successfully Treated Early Hepatocellular Carcinoma Improves Survival in Cirrhotic Patients with Chronic Hepatitis C

- ITAL.ICA, N = 221 consecutive HCV patients
  - BCLC 0/A, complete radiological response after curative resection or ablation, subsequently treated with DAAs
- Median time-lag CR and DAAs starting was 1.7 months (range: 0.5-5.5)
- Median follow-up after DAA 17 months (range 1–34)
- SVR12 85%
- N = 52 recurrences
- OS 97.6% at 1 years and 92.9% at 2 years.
- HCC recurrence rates 7.6% at 6 months, 18% at 1 year, 34.5% at 2 years.
- Longer OS (p<0.0001) and TTR (p=0.008) in SVR12 HR=0.17 (0.05–0.58)
North American multicenter retrospective cohort study, N = 866

HCV-related HCC - CR after resection, ablation, TACE or TARE from 1/2013 to 12/2016.

355 (41.0%) received DAA and 511 (59.0%) were untreated.

HCC recurred in 149 (42.0%) DAA-treated and 300 (58.7%) untreated patients

DAA therapy associated with significantly reduced HCC recurrence risk (HR 0.41, 95% CI 0.32–0.52), adjusting for study site, age, sex, Child Pugh class, AFP level, initial tumor burden and initial HCC therapy

Larger % DAA-treated than untreated patients candidates for potentially curative therapy (transplant, resection or ablation) for HCC recurrence (34.2% vs 25.7%, p=0.06).
UNOS Exception Chances

- HCC patients likely to have longer wait times $\rightarrow$ higher risk of recurrence
  - Need to be more aggressive with curative therapy
  - Need to be more aggressive with LDLT
  - Need to be aggressive in curing HCV
    - DAA associated with less recurrence and more likely to be candidates for curative treatment when recur
  - More likely to remain untransplanted long enough that systemic therapy may be appropriate for bridging (data-free)
Outline

- Primary prevention
- HCC Risk Assessment
- Updates to UNOS Exception Points

**Update in HCC therapy**
- 1\(^{st}\) line approved
- 2\(^{nd}\) line approved options
- What to expect in 2019
Palliation of HCC: Sorafenib

- **SHARP trial**: CTP A pts with advanced HCC randomized to sorafenib 400 BID vs placebo
- Sorafenib delayed progression and prolonged survival from 7.9 to 10.7 mos
- Led to approval by the FDA in 2007 for palliation of advanced-stage HCC

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Phase III REFLECT Study: Frontline Lenvatinib vs Sorafenib in Unresectable HCC

- Randomized, open-label noninferiority phase III trial

  Stratified by region (Asia-Pacific vs Western), MVI and/or EHS (yes vs no), ECOG PS (0 vs 1), body weight (< 60 kg vs ≥ 60 kg)

Pts with unresectable, previously untreated HCC, Child-Pugh A, ECOG PS 0-1 (N = 954)

- Primary endpoint: OS

- Secondary endpoints: PFS, TTP, ORR, PK, QoL

*Body weight < 60 kg, 8 mg; body weight ≥ 60 kg, 12 mg.

Lenvatinib QD* (n = 478)

Sorafenib 400 mg BID (n = 476)

Treatment continued until PD, unacceptable toxicity, or withdrawal of consent.
## Phase III REFLECT Study: Lenvatinib vs Sorafenib in Unresectable HCC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lenvatinib (n = 478)</th>
<th>Sorafenib (n = 476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mos (95% CI)</td>
<td>13.6 (12.1-14.9)</td>
<td>12.3 (10.4-14.9)</td>
</tr>
<tr>
<td>mPFS, mos (95% CI)</td>
<td>7.4 (6.9-8.8)*</td>
<td>3.7 (3.6-4.6)</td>
</tr>
<tr>
<td>mTTP, mos (95% CI)</td>
<td>8.9 (7.4-9.2)*</td>
<td>3.7 (3.6-5.4)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>115 (24.1)*</td>
<td>44 (9.2)</td>
</tr>
</tbody>
</table>

- Noninferior survival
- Inferior PFS and TTP
- Superior objective tumor response by mRECIST
- HRQOL equivalent in most domains except diarrhea

Time to Progression (TTP) and Response Rate (RR) Are Not Reliable Surrogate Endpoints for Overall Survival (OS) in Hepatocellular Carcinoma (HCC): An Analysis from the Phase 3 RESORCE Trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>mOS, days</th>
<th>Simulated data</th>
<th>mTTP, days</th>
<th>Simulated data</th>
<th>RR</th>
<th>Simulated data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SD) of mOS, days</td>
<td>Mean (SD) of mTTP, days</td>
<td></td>
<td></td>
<td>Mean (SD) of RR</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>323</td>
<td>318 (24.3)</td>
<td>119</td>
<td>113 (13.7)</td>
<td>0.066</td>
<td>0.066 (0.0129)</td>
</tr>
<tr>
<td>Placebo</td>
<td>237</td>
<td>236 (21.8)</td>
<td>45</td>
<td>45 (1.2)</td>
<td>0.026</td>
<td>0.026 (0.0113)</td>
</tr>
</tbody>
</table>

mOS, median overall survival; RR, response rate; SD, standard deviation; mTTP, median time to progression.
Nivolumab in Patients with Child-Pugh B Advanced Hepatocellular Carcinoma (aHCC) in the CheckMate-040 Study

- N=49, CTP B7-8
  - SOR-naïve (n=25)
  - SOR-experienced (n=24)
- NIVO 240 mg IV Q2W
- 57.1% BCLC C
- ORR was 10.2% with 5 of 49 patients responding and disease control rate was 55.1%.
- Median DOR was 9.9 mo
- mOS 7.6 mo
- Safety profile comparable to CTP A
- TEAE → discontinuation in 2 pts (hepatotoxicity)

### Safety profile of nivolumab in patients with Child-Pugh B status and Child-Pugh A status in CheckMate-040

<table>
<thead>
<tr>
<th>Drug-related AE</th>
<th>Any grade</th>
<th>Grade 3-4</th>
<th>Any grade</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab 240 mg IV N=49</td>
<td></td>
<td></td>
<td>Nivolumab 0.1–10 mg/kg (ESC) and 3 mg/kg (EXP) N=262</td>
<td></td>
</tr>
<tr>
<td>Drug-related AEs</td>
<td>25 (51.0)</td>
<td>12 (24.5)</td>
<td>206 (78.6)</td>
<td>59 (22.5)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>3 (6.1)</td>
<td>3 (6.1)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Drug-related SAEs</td>
<td>2 (4.1)</td>
<td>2 (4.1)</td>
<td>23 (8.8)</td>
<td>13 (5.0)</td>
</tr>
<tr>
<td>Drug-related AEs leading to discontinuation</td>
<td>2 (4.1)</td>
<td>2 (4.1)</td>
<td>11 (4.2)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Drug-related select hepatic events</td>
<td>4 (8.2)</td>
<td>2 (4.1)</td>
<td>38 (14.5)</td>
<td>18 (6.9)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>2 (4.1)</td>
<td>2 (4.1)</td>
<td>27 (10.3)</td>
<td>15 (5.7)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>1 (2.0)</td>
<td>0</td>
<td>26 (9.9)</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1 (2.0)</td>
<td>0</td>
<td>3 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Liver function test increased</td>
<td>1 (2.0)</td>
<td>0</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>IMAEs – hepatitis</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>14 (5.3)</td>
<td>12 (4.6)</td>
</tr>
</tbody>
</table>

* Select drug-related AEs are those that differ from AEs caused by non-immunotherapies, and may require early intervention to mitigate toxicity and immunosuppression as part of their management; b As reported by investigators; c Where immune modulating medication was initiated. AE, adverse event; ESC, dose-escalation phase; EXP, dose-expansion phase; IMAE, immune-mediated adverse event; NR, not reported; SAE, serious adverse event.
Pembrolizumab

- Key eligibility criteria
  - Aged ≥18 years
  - Pathologically confirmed HCC
  - Progression on or intolerance to sorafenib treatment
  - Child-Pugh class A
  - ECOG PS 0-1
  - BCLC stage C or B disease
  - Predicted life expectancy >3 mos

Pembrolizumab
200 mg q3w
for 2 years or until PD, intolerable toxicity, withdrawal of consent or investigator decision

Survival follow-up

- Response assessed q9w
- Primary endpoint: ORR (RECIST v1.1, central review)
- Secondary endpoint: DOR, DCR, PFS, OS, and safety and tolerability
Pembrolizumab

Median (95% CI) months = NR (9.4-NE)

Overall Survival, %

Time, Months

No. at risk

FDA Approved 11/16/18 2nd line

Zhu Ax, et al. 2018 ASCO-GI #209

<table>
<thead>
<tr>
<th>Response</th>
<th>Total N = 104</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>17 (16.3)</td>
<td>9.8-24.9</td>
</tr>
<tr>
<td>Disease control (CR + PR + SD)</td>
<td>64 (61.5)</td>
<td>51.5-70.9</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (1.0)</td>
<td>0.0-5.2</td>
</tr>
<tr>
<td>PR</td>
<td>16 (15.4)</td>
<td>9.1-23.8</td>
</tr>
<tr>
<td>SD</td>
<td>47 (45.2)</td>
<td>35.4-55.3</td>
</tr>
<tr>
<td>PD</td>
<td>34 (32.7)</td>
<td>23.8-42.6</td>
</tr>
<tr>
<td>No assessment</td>
<td>6 (5.8)</td>
<td>2.1-12.1</td>
</tr>
</tbody>
</table>
Overall Survival and Progression-free Survival
Sorafenib as only prior therapy for HCC

<table>
<thead>
<tr>
<th></th>
<th>Median OS mo (95% CI)</th>
<th>No. of Deaths</th>
<th>Median PFS mo (95% CI)</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib (n=331)</td>
<td>11.3 (9.5-13.9)</td>
<td>219</td>
<td>5.5 (4.6-5.7)</td>
<td>246</td>
</tr>
<tr>
<td>Placebo (n=164)</td>
<td>7.2 (5.8-9.3)</td>
<td>114</td>
<td>1.9 (1.9-1.9)</td>
<td>142</td>
</tr>
</tbody>
</table>

Hazard ratio 0.70 (95% CI 0.55-0.88)
Role of genetic testing in treatment of HCC

Emerging Drugs for HCC

- **MET signaling inhibitors**
  - Tepotinib

- **VEGR2**
  - Ramucirumab

- **FGFR inhibitors**
  - Pan-FGFR inhibitor (erdafitinib)
  - Selective FGFR4 inhibitor (FGF401)

- **TGF-β signaling**
  - Galunisertib

- **Antiangiogenic and antiproliferative TKIs**
  - Donafenib (first line phase III under way: NCT02645981)

- **Immune checkpoint inhibitors**
  - Nivolumab in 1st line (Checkmate-059, NCT02576509)
  - Pexavec (NCT02562755)
  - Durvalumab (anti–PD-L1) + tremelimumab (anti–CTLA-4) (NCT02519348)
  - Atelizumab (anti_PD-L1)+ Bevacizumab (anti-VEGFR)
Ramucirumab (VEGFR2) in 2\textsuperscript{nd} line Phase III

- Two phase III studies (REACH-2 and REACH), Pooled analysis presented
- Sorafenib-intolerant or progressed, AFP \(\geq\)400 ng/mL
- OS 8.1 vs. 5.0 months compared with placebo HR 0.694; 95% CI 0.571, 0.842; \(p=0.002\)
- PFS 2.8 mo vs 1.5 mo PL; HR 0.572; 95% CI 0.472, 0.694; \(p<0.0001\)
- ORR (5.4\% RAM vs 0.9\% PL [\(p=0.0040\)]; DCR (ORR + stable disease = 56.3\% RAM vs 37.2\% PL [\(p<0.0001\)]).
- Higher rate of discontinuation due to TRAE
  - Hypertension (12.0\% vs 3.6\% PL)
  - Hyponatremia (5.1\% vs 2.2\% PL)
- RAM delayed time to deterioration of FHSI-8 (\(p=0.0152\)), including individual items of back pain, weight loss, and pain.

NCT02435433; NCT01140347. Llovet J, AASLD 2018 Abstract #270
New Met inhibitor

- Phase II trial of tepotinib vs sorafenib in Asian patients with aHCC
- Tepotinib - potent and highly selective MET inhibitor
- Patients:
  - Asian adults with MET+ (2+ or 3+ by immunohistochemistry)
  - BCLC B/C
  - CTP A
  - ECOG PS 0 – 1
- Randomized (1:1) to tepotinib 500 mg once daily or sorafenib 400 mg twice daily in 21-day cycles. (tepotinib n = 38, sorafenib n = 37)
- Endpoints: TTP, OS, response
  - TTP longer for tepotinib vs sorafenib (2.8 vs 1.4 months; HR 0.42 (0.26, 0.70); p = 0.0043).
  - Median PFS longer for tepotinib (2.8 vs 1.4 months; HR 0.53 (0.33, 0.84); p = 0.0229)
  - Median OS was similar (tepotinib 9.3 vs sorafenib 8.6 months; HR 0.73 [0.43, 1.12]; p = 0.3039).
  - Similar TEAEs
Atezolizumab + Bevacizumab

- Bevacizumab augment atezolizumab (anti–PD-L1)-mediated anti-tumor immune responses.
- Phase Ib study
- Unresectable or metastatic HCC
- Atezo 1200 mg + bev 15 mg/kg IV q3w as first-line
- ORR per RECIST v1.1, PFS, DOR (RECIST v1.1.)
- Interim: 68 pts
  - Gr 3-4 tx-related AEs were seen in 17 pts (25%)
  - Immune-related AEs in 4 pts (6%)
  - 23/68 responses
  - Median DOR and median OS not yet reached
Systemic therapy

- Now have:
  - 2 First line – TKIs – likely to be differentiated by tolerability
  - 3 2nd line options
    - Regorafenib, Nivolumab, Pembrolizumab
    - Cabozantinib near future
    - Likely ramucirumab
- Just beginning to see combination trial data
**Conclusion**

- Don’t be afraid of ASA and statins in patients with liver disease
- Not all patients with cirrhosis benefit equally from cancer surveillance
  - ? Predictor tools will be accepted tools
- Downstaging HCC according to strict rules work
- All flying out window with new UNOS exception rules
  - Need to really consider early curative options
  - LDLT
  - Cure HCV in HCC
  - ? Bridging therapy to keep patients on list longer
- Expanding armamentarium for advanced disease
  - Optimal sequencing (?)
  - New combinations
Questions