UPDATE ON HEPATOCELLULAR CARCINOMA

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Discussion

- Improvements to HCC screening
- Genetics of HCC
  - Potential treatments
- New approaches to therapy
  - Resection
    - Extended indications
    - Laparoscopic resection
  - TACE
  - Liver transplantation
At risk groups

- Definition of HCC risk
  - Not all patients with cirrhosis will develop HCC
  - Need to identify those with risk high enough to warrant screening

- Defined by cost-efficacy analysis
  - In cirrhosis screening becomes effective and cost effective if HCC incidence > 1.5-2%/year
  - In non-cirrhotic hepatitis B screening becomes effective and cost effective if HCC incidence > 0.2%/year
## Target Populations for HCC Surveillance

<table>
<thead>
<tr>
<th>Population group</th>
<th>Threshold incidence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian male HBV-infected &gt; Age 40</td>
<td>0.2%</td>
<td>0.4-0.6%/yr</td>
</tr>
<tr>
<td>Asian females HBV infected &gt; age 50</td>
<td>0.2%</td>
<td>0.3-0.6%/yr</td>
</tr>
<tr>
<td>HBV carrier with family history of HCC</td>
<td>0.2%</td>
<td>Incidence than without family history</td>
</tr>
<tr>
<td>African/North American Blacks with HBV</td>
<td>0.2%</td>
<td>HCC occurs at a younger age</td>
</tr>
<tr>
<td>Cirrhotic HBV carriers</td>
<td>0.2-1.5%</td>
<td>3-8%/yr</td>
</tr>
<tr>
<td>Hepatitis C cirrhosis</td>
<td>1.5%</td>
<td>3-8%/yr</td>
</tr>
<tr>
<td>Stage 4 PBC</td>
<td>1.5%</td>
<td>3-8%/yr</td>
</tr>
<tr>
<td>Genetic hemochromatosis</td>
<td>1.5%</td>
<td>Unknown but probably &gt; 1.5%/yr</td>
</tr>
<tr>
<td>Alpha 1-antitrypsin deficiency</td>
<td>1.5%</td>
<td>Unknown but probably &gt; 1.5%/yr</td>
</tr>
<tr>
<td>Other cirrhosis</td>
<td>1.5%</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Bruix and Sherman hepatology 2011
<table>
<thead>
<tr>
<th>Baseline Hepatocellular Carcinoma Predictor</th>
<th>Regression Coefficient</th>
<th>Risk Score</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (each 5 years increment)</td>
<td>0.46</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Reference</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.91</td>
<td>2</td>
<td>&lt;0.001</td>
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<tr>
<td>Levels of ALT (IU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15</td>
<td>Reference</td>
<td>0</td>
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</tr>
<tr>
<td>15-44</td>
<td>0.36</td>
<td>1</td>
<td>0.10</td>
</tr>
<tr>
<td>≥ 45</td>
<td>0.76</td>
<td>2</td>
<td>0.01</td>
</tr>
<tr>
<td>Family history of hepatocellular carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.98</td>
<td>2</td>
<td>0.001</td>
</tr>
<tr>
<td>HBeAg/HBV DNA/HBsAg/Genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative/&lt;10^4/&lt;100/any type</td>
<td>Reference</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Negative/&lt;10^4/100-999/any type</td>
<td>0.82</td>
<td>2</td>
<td>0.13</td>
</tr>
<tr>
<td>Negative/&lt;10^4/≥1000/any type</td>
<td>1.07</td>
<td>2</td>
<td>0.04</td>
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<tr>
<td>Negative/10^4−10^6/&lt;100/any type</td>
<td>1.42</td>
<td>3</td>
<td>0.04</td>
</tr>
<tr>
<td>Negative/10^4−10^6/100-999/any type</td>
<td>1.45</td>
<td>3</td>
<td>0.005</td>
</tr>
<tr>
<td>Negative/10^4−10^6/≥1000/any type</td>
<td>1.78</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative/≥10^6/any level/B or B+C</td>
<td>2.45</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative/≥10^6/any level/C</td>
<td>3.09</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive/any level/any level /B or B+C</td>
<td>2.70</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive/any level/any level /C</td>
<td>3.37</td>
<td>7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
REACH-B plus HBsAg

Fig. 2. Cumulative (A) liver cirrhosis and (B) HCC risk by sum risk scores in the validation set.
## LSM-HCC accuracy

<table>
<thead>
<tr>
<th></th>
<th>LSM-HCC score</th>
<th>CU-HCC score</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>95% CI</td>
</tr>
<tr>
<td>3 year prediction</td>
<td>AUROC</td>
<td>0.89</td>
</tr>
<tr>
<td>5 year prediction</td>
<td>0.83</td>
<td>0.71-0.95</td>
</tr>
</tbody>
</table>

Wong et al J Hepat 2014
External validation in CHB

- Independent cohort
  - Mixed ethnic background
  - Tested CU-HCC, GAG-HCC and REACH B and REVEAL nomograms

- Conclusions
  - All models stratified risk of HCC
  - CU-HCC performed best (AUROC 0.85-0.91)
  - Models improved by including additional variables
    - e.g., cirrhosis for REACH-B
    - e.g., Gender for CU-HCC

Predicting HCC risk in Hepatitis C

- MLR variables
  - Age
  - Black race
  - Alkaline phosphatase
  - Esophageal varices
  - Ever smoked
  - Platelets

Lok et al Gastro 2009
HCC risk score by etiology

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt; 45</td>
<td>0</td>
</tr>
<tr>
<td>45-60</td>
<td>4</td>
</tr>
<tr>
<td>&gt;60</td>
<td>8</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Autoimmune</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>6</td>
</tr>
<tr>
<td>HCV</td>
<td>9</td>
</tr>
<tr>
<td>HBV</td>
<td>12</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
</tr>
<tr>
<td>APRI</td>
<td></td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>0</td>
</tr>
<tr>
<td>1.5-4</td>
<td>4</td>
</tr>
<tr>
<td>&gt;4</td>
<td>8</td>
</tr>
</tbody>
</table>
Effect of treatment on HCC risk score in hepatitis B

- Multicenter European study (n=774)
- Baseline GAG-HCC, CU-HCC and REACH-B scores
  - Repeated after 1 year of ETV
    - Only 14 HCC developed
- Conclusions
  - All risk scores decreased
  - Sensitivity for prediction of HCC was variable
    - 11% for GAG-HCC (1/9 subjects)
    - 89% for CU-HCC (8/9 subjects)
    - 50% for REACH-B (4/8 subjects)

Arends et al Gut 2014
HCC risk score after therapy

- HCC after interferon treatment in chronic hepatitis C

Chang et al. Br J Cancer 2013
Summary: Use of risk scores

- Not yet validated
- May serve as a guide
  - Ensure that risk score used is appropriate for that patient
  - Err on the side of caution
Frequency distribution of AFP in HCC by HCC size

Leber, unpublished data
AFP/ALT HCC screening for hepatitis C cirrhosis

Population: Patients with hepatitis C cirrhosis who were diagnosed with HCC within 6 months of testing

HCC probability modified by ALT values

El Serag at al. Gastroenterology 2014
Use of longitudinal AFP data

- Bayesian analysis of prior AFP behaviour
  - With prior normal or low AFP small changes suggests HCC
  - With prior high AFP larger changes suggest HCC

Tayob et al Clin Gastro Hepatol (on line 2015)
Using current biomarkers

- AFP
- AFP-L3
- DCP

Johnson et al. Cancer Epidemiol Biomarkers Prev 2014

Maximum sensitivity 97%
Maximum specificity 80%
Accuracy 88%
HCC STAGING
BCLC staging of HCC

Very early stage (0)
- Single ≤ 2 cm
- Child-Pugh A, PS 0

Potential candidate for liver transplantation
- No
- Yes

Early stage (A)
- Single or 3 nodules ≤ 3 cm
- Child-Pugh A-B, PS 0

Portal pressure, bilirubin
- Normal
- Increased

Intermediate stage (B)
- Multinodular
- Child-Pugh A-B*, PS 0

Advanced stage (C)
- Portal invasion
- Extrahepatic spread
- Child-Pugh A-B*, PS 1-2

Terminal stage (D)
- Child-Pugh C**
- PS 3-4

Treatment
- Ablation
- Resection
- Transplant
- Ablation
- TACE
- Sorafenib
- BSC

Prognosis
- No
- Yes

Associated diseases
- No
- Yes

CURATIVE TREATMENTS
- Palliative TREATMENTS
Hong Kong University Staging System

Yau et al Gastroenterology 2014
PATHWAYS AFFECTING HCC GROWTH AND DEVELOPMENT
Modeling the microenvironment and immune effects

Zucman-Rossi et al Gastro 2015
# DRUGS UNDER TEST FOR HCC

<table>
<thead>
<tr>
<th>TARGETTED AGENTS</th>
<th>EPigenetic MODULATORS</th>
<th>CELL CYCLE INHIBITORS</th>
<th>IMMUNE MODULATORS</th>
<th>PRO-APOPTOTIC AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tivantinib</td>
<td>SGI-110</td>
<td>Refametanib</td>
<td>Nivolumab</td>
<td>Mapatumumab</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>LY2875358</td>
<td></td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>MSC2156119J</td>
<td></td>
<td>Ipilimumab</td>
<td></td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Donafenib</td>
<td></td>
<td>Tasquinomod</td>
<td></td>
</tr>
<tr>
<td>ADI-PEG20</td>
<td>TKM-080301</td>
<td></td>
<td>Pexa-Vec</td>
<td>Icaritin</td>
</tr>
</tbody>
</table>
TREATMENT
Survival in HCC

Overall survival according to tumor classification. *Solid line*: absence of any adverse prognostic factor (48 patients; median survival, 40 months). *Dotted line*: presence of at least one adverse prognostic factor (54 patients; median survival, 5.4 months).

Adapted from Llovet Hepatology 1999
Survival post HCC resection

Ishizawa et al Gastroenterology 2008
The Bridge study

A

P=0.001 A vs. B
A-Ideal candidates resected
B-Ideal candidates not resected
C-Non-ideal candidates resected

P=0.017
B vs. C

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>718</td>
<td>429</td>
<td>266</td>
<td>147</td>
<td>54</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>144</td>
<td>84</td>
<td>50</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1624</td>
<td>836</td>
<td>457</td>
<td>210</td>
<td>71</td>
<td>28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Roayaie et al. Hepatology 2015
Intermediate Stage HCC is heterogeneous

- Single large HCC
- Single small HCC not suitable for resection or ablation (e.g., location)
- Multiple lesions
  - Paucinodular
  - Diffuse
  - Infiltrative

These may have different prognosis
Improved prognostication for intermediate stage HCC

- mHAP-II
  - Albumin < 36 gm/L
  - Bilirubin > 17 umol/L
  - AFP > 400 ng/mL
  - > 2 lesions
  - Size > 7 cm

Park et al Liv Int 2015
Survival according to HAP scores

HAP

mHAP-II

Capelli et al Liv Int 2016
ART score

- Designed to assess prognosis after 1st TACE
  - Criteria
    - Increase in Child-Pugh score
    - Increase in AST > 25%
    - Radiological response
  - 2 prognostic groups
    - Low ART score prognosis ~23 months
    - High ART score prognosis ~3-4 months
  - High frequency of complications from 2nd TACE in high ART score group

Sieghart et al. Hepatology 2013
# Development of the ART score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Response</th>
<th>ART score points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh score Increase</td>
<td>Absent</td>
<td>nil</td>
</tr>
<tr>
<td></td>
<td>+1 point</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>≥ 2 points</td>
<td>3</td>
</tr>
<tr>
<td>AST increase &gt; 25 uL</td>
<td>Absent</td>
<td>nil</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>4</td>
</tr>
<tr>
<td>Radiologic tumour response</td>
<td>Present</td>
<td>nil</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1</td>
</tr>
</tbody>
</table>

Sieghart et al.   Hepatology 2013
Development of the ART score

B

0-1.5 points (n=60): 23.7 [95%CI: 16.2-32.2]
≥2.5 points (n=37): 6.6 [95%CI: 4.5-8.8]
p<0.001
Radioembolization

• Survival

<table>
<thead>
<tr>
<th>Author</th>
<th>Child Pugh A (months)</th>
<th>Child Pugh B (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salem 2009</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>Sangro 2009</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Lewandowski 2009</td>
<td>42</td>
<td>--</td>
</tr>
<tr>
<td>Various authors</td>
<td>Various stratification factors – 5-40 months</td>
<td></td>
</tr>
</tbody>
</table>

• Radiation hepatectomy
TARE for downstaging

<table>
<thead>
<tr>
<th></th>
<th>TACE</th>
<th>TARE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASL CR</td>
<td>17%</td>
<td>47%</td>
<td>0.13</td>
</tr>
<tr>
<td>Downstaged</td>
<td>31%</td>
<td>58%</td>
<td>0.023</td>
</tr>
<tr>
<td>Solitary lesion</td>
<td>21</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Downstaged</td>
<td>28% (n=6)</td>
<td>75% (n=15)</td>
<td>0.005</td>
</tr>
<tr>
<td>Multifocal</td>
<td>14</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Downstaged</td>
<td>36% (n=5)</td>
<td>44% (n=10)</td>
<td>0.74</td>
</tr>
</tbody>
</table>
STOP-HCC Trial

- Unresectable HCC → sorafenib is planned
  - Therasphere (Y90) → sorafenib
  - Sorafenib
- Primary outcome = OS → study visits q8wks
- Inclusion criteria
  - CPA, ECOG ≤1
- Exclusion criteria
  - Main PVT
Radioembolization

- Phase 2 RCT (2 studies)
  - Radioembolization vs chemoembolization
    - End point – time to progression
- Theraspheres vs sorafenib for HCC with portal vein thrombosis
RTOG1112 Trial (NCI)

- HCC unsuitable or refractory to TACE
  - SBRT 27.5-45 Gy in 5# → sorafenib
  - Sorafenib
- Primary outcome = OS
- Inclusion criteria
  - CPA, BCLC B or C, ≥1 lesion or tumour thrombosis
- Exclusion criteria
  - Prior sorafenib, Y90, RT
  - HCC >15, >5 lesions, sum >20cm, EHS >2cm
Conclusions

- Intermediate stage HCC
  - Multifocal HCC
  - Large single HCC not amenable to other curative therapies (stage migration)

- TACE is standard of care
  - No benefit of combination with sorafenib

- TARE and SBRT require further study
  - RCTs with sorafenib underway
THANK YOU FOR YOUR ATTENTION