9th Paris Hepatitis Conference

Paris, 12 January 2016

Treatment of hepatocellular carcinoma: beyond international guidelines

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Financial Disclosures

Grant and research support: BMS, Gilead Science

Advisory committees: Merck, Roche, Novartis, Bayer, BMS, Gilead Science, Tibotec, Vertex, Janssen Cilag, Achillion, Lundbeck, GSK, GenSpera

Speaking and teaching: Tibotec, Roche, Novartis, Bayer, BMS, Gilead Science, Vertex, Merck, Janssen
Treatment of Hepatocellular Carcinoma Beyond International Guidelines

Outline

- Loss of survival benefits in patients treated outside recommendations.
- Local ablation of early cancer is more cost effective than limited resection.
- Can resection in patients with portal hypertension be facilitated by DAAs?
- Can sorafenib therapy scale up in advanced cirrhosis following DAA therapy?
- Reconsidering non transplant therapeutic options in the era of donor shortage.
## Adherence to AASLD Recommendations in the Treatment of HCC. A Study in Milan

<table>
<thead>
<tr>
<th>Reasons for withdrawing from recommendations</th>
<th>Total (No.370)</th>
<th>BCLC A (No. 251)</th>
<th>BCLC B (No. 66)</th>
<th>BCLC C (No. 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired liver function</td>
<td>17 (5%)</td>
<td>0</td>
<td>7 (11%)</td>
<td>10 (19%)</td>
</tr>
<tr>
<td>Strategic localization and/or vascular invasion</td>
<td>53 (14%)</td>
<td>19 (8%)</td>
<td>21 (32%)</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>33 (9%)</td>
<td>28 (11%)</td>
<td>2 (3%)</td>
<td>9 (17%)</td>
</tr>
</tbody>
</table>
Adherence to AASLD Recommendations in the Treatment of HCC. A Study in Milan

- January 2007 to December 2011, 370 de novo HCCs (295 upon surveillance)

- All treated by a MDT according to AASLD criteria

- Overall yearly mortality: 11.5%. 9.8% adherent vs 16.6% non adherent (P=.0042)

- BCLC A (n=251, 81% adherent). Overall yearly mortality: 5.9%. 5.1% adherent vs 10.3% non adherent (P=.0056)

- Multivariate: OS predicted by AASLD adherence (HR 2.1, CI :1.1-4.3), tumor size, ascites.
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**EASL: BCLC Staging System and Treatment Strategy**

**HCC**

1. **Stage 0**
   - Very early stage (0)
     - Single
       - Portal pressure/bilirubin
         - Increased
           - Associated diseases
             - Yes: RF/PEI
               - Target: 20%
               - OS: 20 mo (45-14)
             - No: Resection
               - Curative treatment (30-40%)
               - Median OS > 60 mo; 5-yr survival: 40-70%
     - Normal

2. **Stage A-C**
   - Early stage (A)
     - 3 nodules ≤ 3cm
   - Intermediate stage (B)
     - Multinodular PS 0
   - Advanced stage (C)
     - Portal invasion N1, M1, PS 1-2
   - Terminal stage (D)

3. **Stage D**
   - Best supportive care
     - Target: 10%
     - OS: < 3 mo

Review Three-yr Survival Following Resection or RFA of HCC in Child Pugh A Cirrhosis

<table>
<thead>
<tr>
<th>Tumor</th>
<th>HR No. of patients</th>
<th>Pooled estimate (%)</th>
<th>RFA No. of patients</th>
<th>Pooled estimate (%)</th>
<th>Results (95% CI)</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single, ≤2 cm</td>
<td>1265/1361</td>
<td>89.4 (73.2-98.7)</td>
<td>1411/1477</td>
<td>90.3 (78.3-94.8)</td>
<td>1.11 (1.03-1.19)</td>
<td>0.949 91</td>
</tr>
<tr>
<td>Single, ≤3 cm</td>
<td>480/551</td>
<td>86.3 (73.6-91.6)</td>
<td>1492/1577</td>
<td>92.6 (86.6-93.2)</td>
<td>1.11 (1.03-1.19)</td>
<td>0.004 47</td>
</tr>
<tr>
<td>Single, &gt;3 cm</td>
<td>105/188</td>
<td>56.5 (47.9-64.9)</td>
<td>105/188</td>
<td>56.5 (47.9-64.9)</td>
<td>1.22 (1.06-1.42)</td>
<td>0.007 0</td>
</tr>
<tr>
<td>Two-three, ≤3 cm</td>
<td>37/55</td>
<td>66.4 (50.7-80.4)</td>
<td>86/122</td>
<td>65.1 (53.3-89.5)</td>
<td>1.03 (0.69-1.52)</td>
<td>0.886 55</td>
</tr>
</tbody>
</table>

Radiofrequency is more cost-effective than resection in very early HCC and 2-3 nodules ≤3 cm

Cucchetti et al, J Hepatol 2013;59:300-7
The Founders of BCLC. Staging and Treatment Strategy

Very early (0) → Potential candidate for liver transplantation
   - No → Ablation
   - Yes → Early (A)

Early (A) →
   - Single → Resection
   - Three nodules ≤3 cm →
     - Portal pressure, bilirubin
       - No → OLT
       - Yes →
         - Increased →
           - Associated diseases
             - No → Reection
             - Yes → Ablation
       - Normal →
         - Associated diseases
           - No → Resection
           - Yes → Ablation

Intermediate (B) →
   - Advanced (C) →
   - Terminal (D) →

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Portal Hypertension and Hepatic Resection for Small HCC
A Meta-analysis, 5-year Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>With PH Events</th>
<th>Without PH Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capussotti 2006</td>
<td>70</td>
<td>71</td>
<td>142</td>
<td>14.2%</td>
<td>1.60 [0.90, 2.82]</td>
</tr>
<tr>
<td>Cucchetti 2009</td>
<td>43</td>
<td>58</td>
<td>165</td>
<td>15.2%</td>
<td>1.51 [0.89, 2.57]</td>
</tr>
<tr>
<td>Giannini 2013</td>
<td>23</td>
<td>51</td>
<td>74</td>
<td>9.7%</td>
<td>0.90 [0.40, 2.02]</td>
</tr>
<tr>
<td>Hidaka 2012</td>
<td>33</td>
<td>47</td>
<td>80</td>
<td>11.4%</td>
<td>3.84 [1.89, 7.79]</td>
</tr>
<tr>
<td>Ishizawa 2008</td>
<td>65</td>
<td>250</td>
<td>315</td>
<td>17.8%</td>
<td>1.88 [1.22, 2.88]</td>
</tr>
<tr>
<td>Llovet 1999</td>
<td>27</td>
<td>35</td>
<td>62</td>
<td>7.4%</td>
<td>5.20 [1.94, 13.94]</td>
</tr>
<tr>
<td>Ruzzenente 2011</td>
<td>24</td>
<td>91</td>
<td>115</td>
<td>10.6%</td>
<td>3.17 [1.49, 6.71]</td>
</tr>
<tr>
<td>Santambrogio 2013</td>
<td>33</td>
<td>160</td>
<td>193</td>
<td>13.7%</td>
<td>2.04 [1.13, 3.69]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>565</td>
<td>986</td>
<td>1,551</td>
<td>100.0%</td>
<td>2.07 [1.51, 2.84]</td>
</tr>
</tbody>
</table>

Total events: 318

Heterogeneity: Tau² = 0.10; Chi² = 13.80, df = 7 (P = 0.05); I² = 49%
Test for overall effect: Z = 4.51 (P < 0.00001)

Effect of SVR to P+R on Hepatic Venous Pressure Gradient in HCV Cirrhosis

A study in Melbourne of 47 patients with cirrhosis treated with P+R

Sustained virological responders

Relapsers

Primary non-responders

Significant association between 20% HVPG decline, histological response and SVR

Roberts S et al, Clin Gastroenterol Hepatol 2007;5:932-7
CPT Score Change from Baseline to FU-24 in CPT B/C Patients Who Achieved SVR12 to DAA Therapy

- **CPT B patients (n=187)**
  - 40% (72/180) improved to CPT A
  - 58% (104/180) had no change in CPT class

- **CPT C patients (n=77)**
  - 12% (8/67) improved to CPT A
  - 64% (43/67) improved to CPT B
  - 24% (16/67) had no change in CPT class

*Gane et al, AASLD 2015*
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GIDEON: Treatment Outcome by Child-Pugh Status (3213 Patients, ITT)

Overall survival

Time to tumor progression

Marrero J, ASCO 2013 abs # 4126.
BCLCp C1: Patients BCLC-C under sorafenib treatment with progression due to growth of existing nodules or new intra-hepatic sites.

BCLCp C2: Patients BCLC-C under sorafenib treatment with progression due to new extra-hepatic lesion and/or vascular invasion.

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Drivers of Organ Allocation for Liver Transplantation in Patients with Cirrhosis vs HCC

Urgency: Focused on pretransplant risk of dying; patients with worse outcome on the waiting list are given higher priority for transplantation (based on Child-Pugh or MELD score).

Utility: Based on maximisation of post-transplant outcome, takes into account donor and recipient characteristics: mainly used for HCC since the MELD score poorly predicts post-transplant outcome in HCC due to the absence of donor factors and lack of predicting tumour progression while waiting.

Benefit: Calculated by subtracting to the survival achieved with LT the survival obtained without LT. Ranks patients according to the net survival benefit that they would derive from transplantation and maximise the lifetime gained through transplantation. If applied to HCC without adjustments, it may prioritise patients at highest risk or recurrence.

Modified by Bruix et al, Gut 2014;63:844-55
Surgical Resection for HCC: Moving from What Can Be Done to What is Worth to Be Done

<table>
<thead>
<tr>
<th>Drivers of Treatment Selection</th>
<th>In favor of Transplantation</th>
<th>In favor of Resection</th>
<th>In favor of Ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Age</td>
<td>≤ 70 years</td>
<td>≤ 75 years</td>
<td>no limit</td>
</tr>
<tr>
<td>• Performance Status</td>
<td>any grade (high MELD)</td>
<td>0</td>
<td>0 major</td>
</tr>
<tr>
<td>• Comorbidities</td>
<td>No</td>
<td>no / minor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tumor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Size</td>
<td>single ≤ 5 cm</td>
<td>≥ 3 cm</td>
<td>≤ 3 cm</td>
</tr>
<tr>
<td>• Number</td>
<td>up to 3 nodules ≤ 3 cm</td>
<td>single peripheral / exophytic</td>
<td>up to 3 nodules central, far from vessels, bile tract and viscera</td>
</tr>
<tr>
<td>• Location within liver</td>
<td>any site</td>
<td></td>
<td>absent</td>
</tr>
<tr>
<td>• Vascular invasion (branch / segment)</td>
<td>absent</td>
<td>not relevant by some</td>
<td>not relevant only in anatomic resections</td>
</tr>
<tr>
<td>• Satellites</td>
<td>not counted when &lt; 1 cm</td>
<td>not relevant only in anatomic resections</td>
<td>absent</td>
</tr>
<tr>
<td>• AFP</td>
<td>&lt; 1,000 ng/ml</td>
<td>the lower the better</td>
<td>any level</td>
</tr>
<tr>
<td>• Perceived anti-tumor efficacy</td>
<td>very high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td><strong>Liver disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cirrhosis</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>• Portal hypertension</td>
<td>any</td>
<td>absent / mild</td>
<td>any</td>
</tr>
<tr>
<td>• Bilirubin (NV ≤ 1 mg/dl)</td>
<td>any</td>
<td>normal</td>
<td>normal / ≤ 2 x nv</td>
</tr>
<tr>
<td>• MELD score</td>
<td>any</td>
<td>very low</td>
<td>low</td>
</tr>
</tbody>
</table>

Modified from Romagnoli et al, Hepatology 2015 in press