Liver transplantation: Hepatocellular carcinoma

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18 de marzo 2015
3r Curso Práctico de Transplante de Órganos Sólidos
Barcelona
### Incidence of hepatocellular carcinoma

#### Incidence and mortality of the 6 most common cancers worldwide

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence*</th>
<th>%</th>
<th>Mortality*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1.847</td>
<td>13.0</td>
<td>1.589</td>
<td>19.7</td>
</tr>
<tr>
<td>Breast</td>
<td>1.676</td>
<td>11.9</td>
<td>0.521</td>
<td>12.9</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>1.360</td>
<td>9.7</td>
<td>0.693</td>
<td>8.5</td>
</tr>
<tr>
<td>Prostate</td>
<td>1.111</td>
<td>7.9</td>
<td>0.307</td>
<td>3.7</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.951</td>
<td>6.8</td>
<td>0.723</td>
<td>8.8</td>
</tr>
<tr>
<td>Liver**</td>
<td>0.748</td>
<td>5.6</td>
<td>0.745</td>
<td>9.1</td>
</tr>
<tr>
<td>All sites</td>
<td>12.667</td>
<td>100</td>
<td>7.571</td>
<td>100</td>
</tr>
</tbody>
</table>

*Numbers of cases (in millions)

**Including HCC and cholangiocarcinoma (< 10%)
Prognostic assessment of HCC patients

Factors that affect prognosis

- Stage, aggressiveness and growth rate of the tumor
- Liver function impairment
- General health of the patient
- The specific intervention (therapy)

Case report

Summary of Liver Disease

Male, 41 years old

1993

- Cirrhosis HCV. Treatment INF plus Rivabirin. No SVR.

2008: Control every 6 months

- Low platelets plus increased AFP
- US: segment IV, nodule of 1.1 cm
<table>
<thead>
<tr>
<th></th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>1,5</td>
<td>0 – 2 mg/dl</td>
</tr>
<tr>
<td>ALT</td>
<td>126</td>
<td>&lt; 40 IU/l</td>
</tr>
<tr>
<td>AST</td>
<td>156</td>
<td>&lt; 40 IU/l</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>271</td>
<td>35 – 104 IU/l</td>
</tr>
<tr>
<td>g-glutamyl transpeptidase</td>
<td>98</td>
<td>5 – 36 IU/l</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>40</td>
<td>37 – 53 g/L</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>81</td>
<td>70 – 100%</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>49</td>
<td>36 - 51 %</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>5410</td>
<td>4000 -10000/mm3</td>
</tr>
<tr>
<td>Platelets</td>
<td>98.000</td>
<td>150.000 – 400.000/mm3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.85</td>
<td>0,3 – 1,5 mg/dl</td>
</tr>
<tr>
<td>AFP</td>
<td>430</td>
<td>0- 10 ng/dl</td>
</tr>
</tbody>
</table>
January 2008

- US

Dist = 1.19 cm
Case report

Radiology: MRI

T1-Gd- arterial phase  

T1-Gd- delayed phase
Mass/Nodule on US

< 1 cm

- Repeat US at 4 mo

Growing/changing character
- Investigate according to lesion size

Stable
- Repeat US at 4 mo

1-2 cm

- 4 phase CT/dynamic contrast enhanced MRI

1 or 2 positive techniques*: HCC radiological hallmarks**

Yes
- HCC

No
- Biopsy

> 2 cm

- 4 phase CT/dynamic contrast enhanced MRI

1 or 2 positive techniques*: HCC radiological hallmarks**

Yes
- HCC

No
- Biopsy

Inconclusive

Diagnostic criteria for HCC
EASL/EORTC Guidelines 2012

EASL–EORTC Clinical Practice Guidelines. J Hepatol. 2012:56(4);908-43
Case report
What would you perform to define the treatment decision?

1. HVPG assessment
2. Surgical resection without further studies
3. Transplantation without further studies
4. CT-cHEST scanner plus HVPG assessment
Case report
Results of HVPG and CT-chest scanner

GPVH: 16,5 mmHg

CT-chest scanner: No M1
**BCLC Staging and Treatment Strategy, 2012**

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

Potential candidate for liver transplantation

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

**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

**CURATIVE TREATMENTS**
- Ablation
- Resection
- Transplant
- Ablation

**PALLIATIVE TREATMENTS**
- Chemoembolization
- Sorafenib
- BSC

Curative treatments: Surgical Resection

Prognosis of HCC suitable to resection

Best candidates:
- Solitary HCC
- Child-Pugh A:
  - No portal hypertension (HVPG < 10 mmHg)
  - Normal Bilirubin (< 1 mg/dl)

Curative treatments: Surgical Resection
Metanalysis of the impact of CSPH on postoperative outcomes

### Panel A: 3-year mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>With PH</th>
<th>Without PH</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capucilli 2006</td>
<td>55</td>
<td>66</td>
<td>121</td>
<td>16.4%</td>
</tr>
<tr>
<td>Cucchielli 2009</td>
<td>33</td>
<td>89</td>
<td>122</td>
<td>16.0%</td>
</tr>
<tr>
<td>Gionini 2013</td>
<td>15</td>
<td>53</td>
<td>68</td>
<td>10.1%</td>
</tr>
<tr>
<td>Hidaka2012</td>
<td>24</td>
<td>48</td>
<td>72</td>
<td>11.0%</td>
</tr>
<tr>
<td>Ishiwa 2008</td>
<td>44</td>
<td>136</td>
<td>180</td>
<td>17.3%</td>
</tr>
<tr>
<td>Llovet 1999</td>
<td>24</td>
<td>42</td>
<td>66</td>
<td>6.3%</td>
</tr>
<tr>
<td>Rizzoncini2011</td>
<td>23</td>
<td>44</td>
<td>67</td>
<td>11.2%</td>
</tr>
<tr>
<td>Santambrogio 2013</td>
<td>21</td>
<td>63</td>
<td>84</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

Total (95% CI) 57/4 398 100.0%

Heterogeneity: Tau² = 0.10, Chi² = 13.20, df = 7 (P = 0.07); I² = 47%
Test for overall effect: Z = 4.50 (P < 0.00001)

### Panel B: 5-year mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>With PH</th>
<th>Without PH</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capucilli 2006</td>
<td>70</td>
<td>98</td>
<td>168</td>
<td>14.2%</td>
</tr>
<tr>
<td>Cucchielli 2009</td>
<td>43</td>
<td>89</td>
<td>132</td>
<td>15.2%</td>
</tr>
<tr>
<td>Gionini 2013</td>
<td>23</td>
<td>44</td>
<td>67</td>
<td>9.7%</td>
</tr>
<tr>
<td>Hidaka2012</td>
<td>33</td>
<td>48</td>
<td>81</td>
<td>11.4%</td>
</tr>
<tr>
<td>Ishiwa 2008</td>
<td>65</td>
<td>136</td>
<td>201</td>
<td>17.8%</td>
</tr>
<tr>
<td>Llovet 1999</td>
<td>27</td>
<td>42</td>
<td>69</td>
<td>7.4%</td>
</tr>
<tr>
<td>Rizzoncini2011</td>
<td>24</td>
<td>44</td>
<td>68</td>
<td>10.6%</td>
</tr>
<tr>
<td>Santambrogio 2013</td>
<td>33</td>
<td>63</td>
<td>96</td>
<td>13.7%</td>
</tr>
</tbody>
</table>

Total (95% CI) 565 986 100.0%

Heterogeneity: Tau² = 0.10, Chi² = 13.00, df = 7 (P = 0.07); I² = 49%
Test for overall effect: Z = 4.51 (P < 0.00001)

### Panel C: clinical decompensation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>With PH</th>
<th>Without PH</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodiwi 2012</td>
<td>13</td>
<td>16</td>
<td>29</td>
<td>7.7%</td>
</tr>
<tr>
<td>Bruix 1996</td>
<td>11</td>
<td>15</td>
<td>26</td>
<td>1.8%</td>
</tr>
<tr>
<td>Capucilli 2006</td>
<td>27</td>
<td>99</td>
<td>126</td>
<td>22.1%</td>
</tr>
<tr>
<td>Cucchielli 2009</td>
<td>11</td>
<td>69</td>
<td>80</td>
<td>12.2%</td>
</tr>
<tr>
<td>Hidaka2012</td>
<td>15</td>
<td>40</td>
<td>55</td>
<td>10.4%</td>
</tr>
<tr>
<td>Llovet 2012</td>
<td>3</td>
<td>10</td>
<td>13</td>
<td>1.7%</td>
</tr>
<tr>
<td>Rizzoncini2011</td>
<td>14</td>
<td>44</td>
<td>58</td>
<td>15.5%</td>
</tr>
<tr>
<td>Santambrogio 2013</td>
<td>18</td>
<td>63</td>
<td>81</td>
<td>20.0%</td>
</tr>
</tbody>
</table>

Total (95% CI) 396 722 100.0%

Heterogeneity: Tau² = 0.08, Chi² = 0.29, df = 7 (P = 0.23); I² = 25%
Test for overall effect: Z = 5.31 (P < 0.00001)

For CCLC Staging and Treatment Strategy, 2012

**Very early stage (0)**
- Single < 2cm
- Child-Pugh A, PS 0
- Potential candidate for liver transplantation

**Early stage (A)**
- Single or 3 nodules < 3cm
- Child-Pugh A-B, PS 0
- Single
- Portal pressure, bilirubin
- Normal
- Increased
- Associated diseases
- No
- Yes
- Transplant

**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

**CURATIVE TREATMENTS**

## Curative treatments: Liver Transplantation

### Outcomes applying restrictive selection criteria

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>n</th>
<th>Selection criteria</th>
<th>Recurrence</th>
<th>Survival at 5y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazzaferro, 1996</td>
<td>48</td>
<td>Milan</td>
<td>8%</td>
<td>74%*</td>
</tr>
<tr>
<td>Jonas, 2001</td>
<td>120</td>
<td>Milan</td>
<td>15%</td>
<td>71%</td>
</tr>
<tr>
<td>Cillo, 2004</td>
<td>30</td>
<td>Milan</td>
<td>6.7%</td>
<td>72%</td>
</tr>
<tr>
<td>Herrero, 2008</td>
<td>47</td>
<td>Milan</td>
<td>8.5%</td>
<td>70%</td>
</tr>
<tr>
<td>Mazzaferro, 2009</td>
<td>444</td>
<td>Milan</td>
<td>5.5%</td>
<td>73.3%</td>
</tr>
</tbody>
</table>

* Survival at 4 years  
~ 5-y recurrence rate  
¬ 100-(5-y RFS)
Curative treatments: Liver Transplantation
Prognosis of patients with HCC waiting for OLT

- Time
- Size
- AFP
- Liver function / MELD

Curative treatments: Liver Transplantation
Prognosis of patients with HCC waiting for OLT

Tumor markers for prognosis assessment

AFP is a criteria for liver transplantation for HCC

AFP < 100 ng/mL
AFP 100-1000 ng/mL
AFP > 1000 ng/mL

Table 2. Simplified, User-Friendly Version of the AFP Model

<table>
<thead>
<tr>
<th>Variables</th>
<th>$\beta$ coefficient</th>
<th>Hazard ratio</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest diameter, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3-6</td>
<td>0.272</td>
<td>1.31</td>
<td>1</td>
</tr>
<tr>
<td>$&gt;$6</td>
<td>1.347</td>
<td>3.84</td>
<td>4</td>
</tr>
<tr>
<td>Number of nodules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>$\geq$4</td>
<td>0.696</td>
<td>2.01</td>
<td>2</td>
</tr>
<tr>
<td>AFP level, ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$100</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>100-1000</td>
<td>0.668</td>
<td>1.95</td>
<td>2</td>
</tr>
<tr>
<td>$&gt;$1000</td>
<td>0.945</td>
<td>2.57</td>
<td>3</td>
</tr>
</tbody>
</table>

Cirrhotic patients with early HCC waiting for cadaveric liver transplantation

- Increase pool of donors
- Priority policies: Is MELD fair/effective?
- Adjuvant treatment during waiting time

Living donor liver transplantation
Domino/Split liver transplantation
High risk donors

Phase II trials

- Chemotherapy
- TACE
- PEI / RF

Cost-efficacy studies

- Resection/PEI
Cirrhotic patients with early HCC waiting for cadaveric liver transplantation

- Increase pool of donors
- Priority policies: Is MELD fair/effective?
- Adjuvant treatment during waiting time

Living donor liver transplantation
Domino/Split liver transplantation
High risk donors

Phase II trials
- Chemotherapy
- TACE
- PEI/RF
- Resection/PEI

Cost-efﬁcacy studies

There are not randomized-controlled trials
Adjuvant treatment during waiting time

Benefit of treatments depends on the waiting time

- Porrett post-MELD (54d)
  - Oldhafer (118d)
  - Decaens (128d)
  - Roayaie (142d)

+ Graziadei (178d)
  + Yao (180d)
  + Maddala (211d)
  + Fisher (277d)

- Hayashi (343d)
  - Porrett pre-MELD (574d)
Case report
Treatment

- Laparoscopy, RFA
- Inclusion in waiting list for Liver transplantation
Case report
Evolution during the waiting list

Imaging follow-up every 3 months: Complete response
Liver donor liver transplantation
Barcelona-Clínica Liver Cancer (BCLC) Group
Head: Jordi Bruix

**Hepatology:** A. Forner, M. Reig, A. Liccioni, A. Gazzola, R. Di Donato


**Surgery:** J. Fuster  
**Pathology:** M. Solé, R. Miquel  
**Oncology:** J. Maurel

**Translational research lab:**
JM. Llovet  
V. Tovar  
J. Peix  
H. Cornellà  
A. Moeini  
C. Alsinet

**Global BCLC lab:**
L. Boix, A. Rhodes, JM. Lopez

**Research Nurse:** N. Llarch

**Study Coordinator:** I. Rengel

**Adm. Support:** N. Pérez  
A. Farré