Hepatocellular carcinoma: Algorithms of diagnosis and options of therapy

Alejandro Forner
BCLC Group. Liver Unit.
Hospital Clinic. University of Barcelona

Pathogenesis and Clinical Practice in Gastroenterology
<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence*</th>
<th>%</th>
<th>Mortality*</th>
<th>%</th>
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<tbody>
<tr>
<td>Lung</td>
<td>1.350</td>
<td>12.4%</td>
<td>1.180</td>
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<td>Breast</td>
<td>1.150</td>
<td>10.6%</td>
<td>0.411</td>
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<td>Colon/rectum</td>
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<td>9.4%</td>
<td>0.529</td>
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<td>Stomach</td>
<td>0.934</td>
<td>8.6%</td>
<td>0.700</td>
<td>10.4%</td>
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<td>Prostate</td>
<td>0.679</td>
<td>6.2%</td>
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<td>Liver**</td>
<td>0.626</td>
<td>5.7%</td>
<td>0.598</td>
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<tr>
<td>ALL SITES</td>
<td>10.887</td>
<td>100%</td>
<td>6.705</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Numbers of cases (in millions)
** Including HCC and cholangiocarcinoma (<10%)

Parkin et al. CA Cancer J Clin, 2005
Diagnosis of cirrhosis

Would the patient be treated if diagnosed with HCC?

Cirrhosis is the main risk factor:

# 5-year incidence 15-20%
# First cause of death

Radical treatments are only possible if HCC is diagnosed at an early stage

Diagram:

Diagnosis of cirrhosis

Would the patient be treated if diagnosed with HCC?

Surveillance (US/6 months)

Bruix & Sherman. Hepatology 2005
Diagnostic criteria for HCC

AASLD Guidelines 2005
EASL-AASLD-J SH Conference on HCC. Barcelona, 2005

- Nodules < 10 mm: Close follow-up

- Nodules 10-20 mm:
  - Non-invasive criteria: Specific vascular pattern in two dynamic techniques (CE-US, CT, MRI)
  - FNB: if atypical vascular pattern in one or both dynamic imaging techniques

- Nodules > 20 mm:
  - Non-invasive criteria: Specific vascular pattern in one dynamic technique
  - FNB: if atypical vascular pattern in dynamic imaging

AFP: no value

Bruix & Sherman. Hepatology 2005
Diagnosis for HCC

Material and methods

Focal lesion 5-20 mm

1\textsuperscript{st} FNB

- Positive
- Negative

2\textsuperscript{nd} FNB

- Positive
- Negative

3\textsuperscript{rd} FNB

- Presence
- Increased Size
- Increased AFP
- Hypervascularity

- Absence

Dynamic MRI + CE-US

- Positive
- Negative

Hypervascularity

CE-US/3 months
Dynamic MRI/6 months

Final diagnosis
### Diagnostic accuracy of CE-US and MRI for HCC <20mm

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>Suspicious</td>
<td>78.3%</td>
<td>86.2%</td>
<td>92.2%</td>
<td>71.4%</td>
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<tr>
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<td>51.7%</td>
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<td>93.9%</td>
<td>50.9%</td>
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<td><strong>MRI</strong></td>
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<tr>
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<td>85%</td>
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<td>61.7%</td>
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<td>54.9%</td>
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<tr>
<td><strong>Both</strong></td>
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</tr>
<tr>
<td>Suspicious</td>
<td>66.7%</td>
<td>100%</td>
<td>100%</td>
<td>59.2%</td>
</tr>
<tr>
<td>Conclusive</td>
<td>33.3%</td>
<td>100%</td>
<td>100%</td>
<td>42%</td>
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</table>

**Suspicious:** Arterial uptake with or without venous *washout*

**Conclusive (AASLD):** Arterial uptake with *washout*

Forner AASLD 2006
### Diagnostic accuracy of CE-US and MRI for HCC \( \leq 20\text{mm} \)

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**Suspicious**: Arterial uptake with or without venous *washout*

**Conclusive (AASLD)**: Arterial uptake with *washout*

Forner AASLD 2006
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)
# Prognostic scoring systems for HCC

<table>
<thead>
<tr>
<th>Author, yr</th>
<th>n</th>
<th>Tumor stage</th>
<th>Liver function</th>
<th>Health status</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Calvet, 1990</td>
<td>206</td>
<td>Tumor size, M1</td>
<td>Bilirubin, Ascites</td>
<td>PST, Age</td>
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<td>Portal thrombosis, AFP</td>
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**BCLC Staging and Treatment Strategy**

- **Stage 0**: PST 0, Child-Pugh A
  - Very early stage (0): Single < 2 cm
  - Early stage (A): Single or 3 nodules < 3 cm, PS 0
  - Portal pressure/ bilirubin: Normal
  - Associated disease: Increased
  - Treatment: Resection or Liver Transplantation (CLT / LDLT)

- **Stage A - C**: Okuda 1-2, PST 0-2, Child-Pugh A-B
  - 3 nodules ≤ 3 cm
  - Treatment: Resection PEI/RF

- **Terminal stage (D)**: Okuda 3, PST > 2, Child-Pugh C

**Curative Treatments**
- 50% - 75% at 5 years

**Endorsed by EASL and AASLD**

*Sem Liv Dis 1999 to Hepatology 2005*
Survival after surgical resection

**Best candidates for resection:**
- Solitary HCC
- Child-Pugh A: No portal hypertension
  Normal bilirubin

![Graph showing survival rates post-surgical resection]

- No portal hypertension (n=35) - 74% survival at 5 years
- Portal hypertension and normal bilirubin (n=15) - 50% survival at 5 years
- Portal hypertension and Bilirubin >1 mg/dL (n=27) - 25% survival at 5 years

Log Rank 0.00001

Llovet et al. Hepatology, 1999
Surgical Resection for HCC
Early vs late recurrence (n=249)

HCC recurrence 184 (72%)

Early recurrence (< 2yr) 123 (67%)
- Microscopic vascular invasion
- Satellites, AFP levels
- Non-anatomical resection

Late recurrence (≥ 2yr) 61 (33%)
- Hepatitis activity
- Gross classification
- Multinodular HCC

Imamura, J Hepatol 2003
## Liver Transplantation for HCC

Outcome applying restrictive selection criteria

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Selection criteria</th>
<th>Survival 1yr</th>
<th>Survival 5yr</th>
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<tr>
<td>Yokoyama, 1990</td>
<td>28</td>
<td>Single ≤ 5cm</td>
<td>77%</td>
<td>68%</td>
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<td>Mc Peacke, 1993</td>
<td>14</td>
<td>Single ≤ 4 cm</td>
<td>85%</td>
<td>57%</td>
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<td>Mazzaferro, 1996</td>
<td>48</td>
<td>Single ≤ 5cm, 3 Nodules ≤ 3cm</td>
<td>90%</td>
<td>75%*</td>
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<td>Llovet, 1998</td>
<td>58</td>
<td>Single ≤ 5cm</td>
<td>84%</td>
<td>74%</td>
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<td>Bismuth, 1999</td>
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<td>Single ≤ 5cm, 3 Nodules ≤ 3cm</td>
<td>82%</td>
<td>74%</td>
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* 4-yr survival

**Best selection criteria for OLT**

- Single HCC ≤ 5 cm / 3 nodules ≤ 3cm
- Absence of vascular invasion / extrahepatic spread
Liver Transplantation for HCC
Prognosis of HCC suitable to OLT

Progression during the waiting time

Time on the waiting list

AJT, Freeman et al 2006
Liver Transplantation for HCC
Strategies to decrease drop-out rate

Cirrhotic patients with early HCC waiting for cadaveric liver transplantation

- Increase pool of donors
- Priority policies
- Adjuvant treatment during waiting time

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

- Chemotherapy: Not effective
- TACE: Absence of RCT
- Ethanol injection Radiofrequency
Percutaneous Ablation for HCC

- Options based on injection of agents or temperature modification
- RF provides better local control than PEI
- Efficacy is the same in HCC ≤ 2cm
- RF is more active in HCC > 2cm. (>3 cm?)
- RF has more severe side effects. Risky locations
- Survival after RF > PEI in Asian RCTs
- No large RCT of surgery vs ablation
- Child-Pugh A with CR: 50% survival at 5 years

Percutaneous Ablation for HCC

Survival according to treatment response and liver function (n= 270)

Survival (%)  
97%  64%  44%  17%  6%  

log rank = .00001

Patients at risk  
Child A  CR  132  119  86  51  35  19  10  
Child A  F  56  40  21  11  8  2  1  
Child B  CR  55  42  28  18  11  4  2  
Child B  F  27  17  7  3  1  

Percutaneous Ablation for HCC

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Sala et al. Hepatology 2004
BCLC Staging and Treatment Strategy

HCC

Stage A - C
Okuda 1-2, PST 0-2, Child-Pugh A-B

Intermediate stage (B)
Multinodular, PS 0

Chemoembolization

Randomized controlled trials
40% - 50% at 3 yr

Endorsed by EASL and AASLD

Sem Liv Dis 1999 to Hepatology 2005
### Cumulative meta-analysis of 6 RCT: TACE vs control

<table>
<thead>
<tr>
<th>Author, Journal year</th>
<th>Cumulative (pts)</th>
<th>OR (95% IC)</th>
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<td>Lin, Gastroenterology 1988</td>
<td>63</td>
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<td>GETCH, NEJM 1995</td>
<td>159</td>
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<td>Bruix, Hepatology 1998</td>
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<td>Pelletier, J Hepatol 1998</td>
<td>312</td>
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<td>OVERALL</td>
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<td><img src="#" alt="Graph showing OR for overall analysis" /></td>
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Heterogeneity: $Q: 7.73, P=0.14$

Llovet and Bruix. Hepatology, 2003
BCLC Staging and Treatment Strategy

HCC

Stage A - C
Okuda 1-2, PST 0-2, Child-Pugh A-B

Advanced stage (C)
Portal invasion, N1,M1, PS 1-2

Portal invasion, N1,M1
No Yes

New Agents

Randomized controlled trials vs 10% at 3yr

Endorsed by EASL and AASLD
Molecular targeted therapies in HCC

Growth factors receptor pathway

Targets and agents

**EGFR:**
- TKI: erlotinib, lapatinib, gefitinib
- Ab: cetuximab

**VEGF**
- TKI: sorafenib
- Ab: bevacizumab

**RAF**
- TKI: sorafenib

**mTOR**
- rapamycin

**Proteasome inhibitors**
- bortezomib

---

Courtesy: A Villanueva
# Treatment of advanced HCC

## Molecular targeted agents

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Action</th>
<th>Phase of study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tyrosine kinase inhibitors and antiproliferative agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sorafenib</td>
<td>RAF inhibitor/VEGF inhibitor (TKI)</td>
<td>III- positive</td>
</tr>
<tr>
<td>- Seocalcitol</td>
<td>Vit-D like antiproliferative</td>
<td>III- negative</td>
</tr>
<tr>
<td>- Erlotinib/Gefitinib</td>
<td>EGFR inhibitor (TKI)</td>
<td>III- design</td>
</tr>
<tr>
<td>- Cetuximab</td>
<td>EGFR inhibitor (Ab)</td>
<td>II- ongoing</td>
</tr>
<tr>
<td>- Lapatinib</td>
<td>EGFR/Her2/neu inhibitor (TKI)</td>
<td>II- ongoing</td>
</tr>
<tr>
<td><strong>Anti angiogenic agents</strong></td>
<td></td>
<td></td>
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<tr>
<td>- Bevacizumab</td>
<td>VEGF inhibitor (Ab)</td>
<td>II - ongoing</td>
</tr>
<tr>
<td>- Thalidomide</td>
<td>Antiangiogenic</td>
<td>III- ongoing</td>
</tr>
<tr>
<td><strong>Other molecular targeted therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bortezomib</td>
<td>Proteasome inhibitor</td>
<td>II- ongoing</td>
</tr>
<tr>
<td>- Nolatrexed</td>
<td>Thymidylate synthase</td>
<td>III- negative</td>
</tr>
<tr>
<td>- T138067</td>
<td>Tubulin inhibitor</td>
<td>III- negative</td>
</tr>
</tbody>
</table>
Phase III SHARP Trial

Study design

International, multicentre, Phase III study

- **Inclusion criteria:**
  - Histology proven HCC
  - Advanced HCC
  - At least one measurable untreated lesion
  - ECOG 0-2
  - Child-Pugh A class
  - No prior systemic treatment

- Double-blind placebo-controlled trial; Ratio 1:1
- Accrual: March 2005 to April 2006
International, multicentre, Phase III study

• Histology proven HCC
• Advanced HCC
• At least one measurable untreated lesion
• ECOG 0-2
• Child-Pugh A class
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• Double-blind placebo-controlled trial; Ratio 1:1
• Accrual: March 2005 to April 2006

EARLY TERMINATION FEBRUARY 2007

SORAFENIB IMPROVES SURVIVAL
Phase III SHARP Trial

Overall survival (Intention-to-treat)

Sorafenib
Median: 46.3 weeks (10.7 mo)
(95% CI: 40.9, 57.9)

Placebo
Median: 34.4 weeks (7.9 mo)
(95% CI: 29.4, 39.4)

Hazard ratio (S/P): 0.69  (95% CI: 0.55, 0.88).
P=0.00058*

*O'Brien-Fleming threshold for statistical significance was P=0.0077.
Probability of progression

Hazard ratio (S/P): 0.58  (95% CI: 0.44, 0.74)

P=0.000007

Sorafenib
Median: 24.0 weeks (5.5 mo)
(95% CI: 18.0, 30.0)

Placebo
Median: 12.3 weeks (2.8 mo)
(95% CI: 11.7, 17.1)

Hazard ratio (S/P): 0.58  (95% CI: 0.44, 0.74)
P=0.000007

Patients at risk
Sorafenib: 299  196  126  80  50  28  14  8  2  0
Placebo: 303  192  101  57  31  12  8  2  1  0
Phase III SHARP Trial

Conclusions

• Sorafenib prolonged overall survival vs placebo in advanced HCC

  Median OS 46 weeks vs 34 weeks
  
  HR 0.69, \( P=0.00058 \)

  44% increase in overall survival

• Sorafenib prolonged time to progression vs placebo

  Median TTP 24 weeks vs 12 weeks
  
  HR 0.58, \( P=0.000007 \)

  73% prolongation in time to progression

• Sorafenib was well-tolerated with manageable side effects
BCLC Staging and Treatment Strategy

HCC

Stage A - C
Okuda 1-2, PST 0-2, Child-Pugh A-B

Advanced stage (C)
Portal invasion, N1,M1, PS 1-2

Portal invasion, N1,M1
No
Yes

Sorafenib

Controlled trials vs 10% at 3 yr

Endorsed by EASL and AASLD

Sem Liv Dis 1999 to Hepatology 2005
BCLC Staging and Treatment Strategy

HCC

Stage D
Okuda 3, PST >2, Child-Pugh C

Terminal stage (D)

Symptomatic treatment

Endorsed by EASL and AASLD
Sem Liv Dis 1999 to Hepatology 2005
Take home messages

- Confident diagnosis of HCC in cirrhotics may be obtained without requesting biopsy; the value of contrast wash-out
- Prognostic estimation is mandatory: BCLC staging
- Early HCC are suitable to radical treatments: Surgical resection, OLT and ablation
- Intermediate stage: TACE
- Advanced stage: Sorafenib
- Terminal stage: Avoid unnecessary suffering
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