State of the Art Lecture:
Hepatocellular Carcinoma: Surgery, Embolization or Drug Therapy – How to Tailor Treatment to the Patient

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Dr. Herrera has indicated no relevant financial relationships.

Hepatocellular Carcinoma: Surgery, Embolization or Drug Therapy: How to Tailor Treatment to the Patient

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Annual Age-Adjusted Incidence per 100,000 of HCC 1975-2005 – United States


Tailored Approach to HCC

- Staging the Patient
  - The Barcelona Clinic Liver Cancer Staging System (BCLC)
- Treatment options
- Putting it all together
  - Matching therapy options with individual patients
Individualized Patient Management

Step #1
Assess Patient Status
History and Physical
## ECOG Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>Performance Status (PS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, no restrictions</td>
</tr>
<tr>
<td>1</td>
<td>Ambulatory, no strenuous activities</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory, capable of self-care, no work activities</td>
</tr>
<tr>
<td>3</td>
<td>Only limited self-care, confined to bed/chair &gt;50%</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled, no self-care</td>
</tr>
</tbody>
</table>


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## Step #2

**Assess Tumor Bulk**

CT / MRI
Tumor Bulk

Curative Options
- Milan Criteria
  - Single <5cm, or ≤ 3 nodules each ≤ 3cm (Milan Criteria)

Palliative Options
- Multinodular with increased tumor bulk
- Portal invasion
- Extrahepatic spread


Therapeutic Options

Curative
- Transplantation
- Resection
- Ablation

Palliative Options
- Radiologic
- Medical
- Terminal care

ECOG PS 0-1
- Small tumors
- No portal invasion
- No extrahepatic spread

ECOG >2
- Larger tumors
- Multinodular tumors
- Portal vein invasion

Rodriguez de Lope C, et al. J Hepatol 2012;S75-587
### Assess Liver Reserve and Portal Pressure

#### Laboratory / Endoscopy / Radiology

#### Liver Reserve

**Child-Pugh-Turcotte Score**

<table>
<thead>
<tr>
<th></th>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dl)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Minimal</td>
<td>Moderate</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>PT (sec prolonged)</td>
<td>&lt;4</td>
<td>4-6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>

**Class A:** 5-6 points  **Class B:** 7-9 points  **Class C:** 10-15 points

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Portal Hypertension

- Esophageal varices
- Platelet count <100,000/mm$^3$ + splenomegaly
- Ascites, present or controlled

**OR**

- Elevated HVPG
  - >10 mmHg

Curative Options

1. Liver Transplantation
2. Resection
3. Ablation
Liver Transplantation

Advantages

- Removes tumor
- Removes oncogenic liver
- Restores liver function
- Available for patients with poor liver function and portal hypertension

Disadvantages

- Only effective in early disease
- Must be operative candidate
- Risk of recurrence (~15%)
- Organ availability
- Waiting period tumor progression


Liver Transplantation

- Strategies to overcome disadvantages
  - Living donor transplant
    - Donor complications 20-40%, mortality 0.3-0.5%
  - Temporizing therapies during waiting period
    - TACE (benefit if waiting >6m)
    - Ablation
    - Sorafenib (experimental)
  - Priority listing for transplantation

Sarasin FP, et al. Hepatology 2001;33;1073-1079
HCC – Priority Listing

- Tumor bulk meets Milan criteria
  - Single lesion <5cm
  - Up to 3 lesions each ≤3 cm
- MELD exception points

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MELD points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single lesion, &lt;2cm</td>
<td>0</td>
</tr>
<tr>
<td>≥2cm</td>
<td>22</td>
</tr>
<tr>
<td>Waiting period</td>
<td>10% increase per 3 months</td>
</tr>
</tbody>
</table>

Bruix J, Sherman M. Hepatology 2010;52:1-35

Resection

Advantages
- No waiting time
- Provides tissue for prognostication
  - Microvascular invasion
  - Microsatellites
- Mortality 1% - 3%

Disadvantages
- Oncogenic liver remains
  - 70% recurrence at 5 years
- Only 5% in Western countries are suitable
  - Child’s Pugh A
  - No portal hypertension (<10 mmHg HVPG)
  - Normal bilirubin

Lencioni R. Hepatology 2010;52:762-773
Ablation

**Advantages**
- Possible in non-operative candidates
- Avoids anesthesia
- Potentially outpatient procedure

**Disadvantages**
- Best for tumors ≤ 2cm, possible up to 5cm
- Leaves oncogenic liver behind
- No tissue for prognostic information
- Potential for seeding of tract
- Less effective if
  - Subcapsular tumor
  - Near gallbladder
  - Near major vessel

Lencini R, Hepatology 2010;52:762-773
Bruix J, Sherman M. Hepatology 2010;52:1-36

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Curative Therapies

<table>
<thead>
<tr>
<th>Modality</th>
<th>5 year survival</th>
<th>5 year recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant</td>
<td>70%-75%</td>
<td>~15%</td>
</tr>
<tr>
<td>Resection</td>
<td>50% - 70%</td>
<td>70%</td>
</tr>
<tr>
<td>Ablation</td>
<td>70% (tumors &lt;2cm)</td>
<td>73%</td>
</tr>
</tbody>
</table>

**Transplant** - ideal option; organ availability is limiting factor
**Resection** – CP-A, no portal hypertension, no comorbidities
**Ablation** – Early disease + comorbidities

Bruix J, Sherman M. Hepatology 2010;52:1-35
Fan ST. Nat Rev Gastroenterol Hepatol 2012;9:732-737
Resection vs. Ablation for HCC

- 12,968 Japanese patients with HCC treated with resection, PEI, or RFA (Nationwide survey, retrospective)

**SURVIVAL:**

![Survival graph]


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Resection vs. Ablation for HCC

- 12,968 Japanese patients with HCC treated with resection, PEI, or RFA (Nationwide survey, retrospective)

**TIME TO RECURRENCE:**

![Recurrence graph]

Palliative Options

- **Image guided transcatheter tumor therapy**
  - TACE (adriamycin, doxorubicin or cisplatin)
  - Radioembolization (Yttrium-90)
- **Medical Therapy**
  - Sorafenib

### Advantages
- 16% to 60% obtain a response (~ 50%)
- Improved survival
  - 16 m → >20 m
- Best results in CP-A
- “Temporizing” tool

### Disadvantages
- Tumor regrowth
- Not well standardized
- Not safe in decompensated liver disease
  - Less benefit in CP-B
- Not safe if portal vein thrombosis
- Not useful if extrahepatic tumor spread
- Post TACE syndrome

Lo CM et al. Hepatology 2002;35:1164-1171
TACE – New Developments

- Polyvinyl alcohol spheres that provide calibrated vessel obstruction
  - Permanent occlusion
- Drug-eluting beads (doxorubicin)
  - Lower systemic chemotherapy side effects
  - Possible improved survival
- Combination with sorafenib


Radioembolization (Yttrium-90)

**Advantages**
- May be used in portal vein thrombosis
- Appears safe
- May be best option in CP-A patients with large tumors

**Disadvantages**
- No RCT confirming efficacy and safety
- Cannot be used if hepatopulmonary shunt
- Risk of depositing spheres in the GI tract
- Post treatment radiation hepatitis
  - 20% grade 3/4 hyperbilirubinemia

Radioembolization — $^{90}$Y Beads

<table>
<thead>
<tr>
<th>TheraSpheres</th>
<th>SIR-Spheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Glass beads (20-30μm)</td>
<td>- Resin beads (20-60 μm)</td>
</tr>
<tr>
<td>- Minimally embolic</td>
<td>- Moderately embolic</td>
</tr>
<tr>
<td>- Lower number of spheres</td>
<td>- Higher number of spheres</td>
</tr>
<tr>
<td>- Higher specific activity</td>
<td>- Lower specific activity</td>
</tr>
</tbody>
</table>

Considered investigational by current clinical guidelines

Ibrahim SM, et al. World J Gastroenterol 2008;14;1664-1669

Sorafenib

- Oral multikinase inhibitor
- Indicated for
  - Failed TACE
  - TACE contraindicated
  - Patient Child-Pugh A or B+
- Partial response in <5%, but decreases time to progression and prolongs survival
  - TTP 2.8m placebo vs. 5.5m sorafenib
  - Median survival 7.9m vs. 10.7m

Sorafenib in Advanced HCC "SHARP Trial"

Time to Progression

Overall Survival


Sorafenib - Toxicity

- Diarrhea, fatigue, weight loss, hand-foot reaction (HFR), hypophosphatemia
- Grade 3/4 AE 11% sorafenib vs. 2% placebo
- HFR (8% vs. 1%)
- Drug discontinuation due to AE - 11%

Sorafenib – Unexplored Options

- Use in BCLC intermediate stage (B)
- Use in combination with TACE*
- Use in combination with $^{90}$Y
- Use in combination with RFA
- Post-transplant to reduce recurrence

*Chao Y, et al. 2011; 5th Annual Conference of Liver Cancer Association, Hong Kong

Putting it All Together

Tailoring the Treatment to the Patient
Very Early Stage Tumor (Stage 0)
Single tumor, <2cm, CP A, PS 0

Curative therapy possible

Liver Transplant / surgical candidate?

NO

Ablation

YES

Bilirubin normal
HVPG <10 mmHg

Resection or transplant

NO

Transplant

Early Stage Tumor (Stage A)
Single >2cm, <5cm or <3 nodules <3 cm, CP – A, PS0

Single nodule

HPVG <10 mmHg
Normal bilirubin

Resection

Transplantation

2 to 3 nodules <3cm

Transplantation

Not a surgical candidate?

Ablation/TACE
Intermediate Stage (Stage B)

- Heterogeneous group
- Child’s Pugh A or B
- Large (>5cm) single tumor or multifocal
- No cancer symptoms
- No macrovascular invasion
- No extrahepatic spread
Advanced Stage (Stage C)

Portal invasion, extra-hepatic spread, CP: A or B, PS: 1-2

Sorafenib

Terminal Stage (Stage D)

Child-Pugh C; PS 3-4

Supportive palliative care
Summary: Individualized Approach Using the BCLC Classification

Stage B
PS 0, Child-Pugh A

Stage A - C
PS 0-2, Child-Pugh A-B

Stage D
PS >2, Child-Pugh C

Very early stage (0)
Single, 2cm

Early stage (A)
Single or 3 nodules < 3cm, PS 0

Intermediate stage (B)
Multinodular, PS 0

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

Terminal stage (D)

Symptomatic treatment

Resection, Liver Transplantation
Curative treatments

RFA, TACE, Sorafenib
Palliative treatments