Liver Transplant for Hepatocellular Carcinoma
Transplant for HCC: BCLC Staging System

Hepatocellular Carcinoma

- Very early stage (0)
  - Single ≤ 2cm
  - Preserved liver function, ECOG PS 0
  - Potential candidate for liver transplantation

- Early stage (A)
  - Single or up to 3 nodules ≤ 3cm
  - Preserved liver function, ECOG PS 0
  - Solitary

- Intermediate stage (B)
  - Multinodular
  - Preserved liver function, ECOG PS 0
  - Up to 3 nodules (≤3 cm)

- Advanced stage (C)
  - Portal invasion
  - Extrahepatic spread
  - Preserved liver function, ECOG PS 1-2

- Terminal stage (D)
  - End-stage liver function*, ECOG PS 3-4

Prognosis:

- No
- Yes
- Portal pressure
  - Bilirubin
    - Normal
    - Increased
      - Associated diseases
        - No
        - Yes
          - Ablation
          - Resection
          - Transplantation

Survival Treatment:

- Ablation
- Resection
- Transplantation
- Ablation
- Chemoembolisation
- Systemic therapy†
- Best supportive care

Effective treatments with impact on survival:

- >5 years
- >2-5 years
- >1 year
- 3 months
## Milestones in Liver Surgery

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langenbuch</td>
<td>1887</td>
<td>1st successful resection</td>
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<td>Keen</td>
<td>1892</td>
<td>1st liver resection series</td>
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<td>Lortat-Jacob</td>
<td>1952</td>
<td>1st anatomic resection</td>
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<td>Quattlebaum</td>
<td>1952</td>
<td>1st US anatomic resection</td>
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<tr>
<td>Longmire</td>
<td>1961</td>
<td>Technical advances</td>
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<tr>
<td>Starzl</td>
<td>1963</td>
<td>First human OLT</td>
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</table>
Liver Transplant for HCC in cirrhosis
Milan Criteria (Stage I+II)

- Single, not > 5cm
- Up to 3, none > 3cm

+ Absence of Macroscopic Vascular Invasion
  Absence of Extrahepatic Spread

UNOS MELD Exception for HCC

Key Points

- LI-RADS-5 (definite HCC) and OPTN 5 lesions must meet nearly identical combinations of imaging criteria: arterial phase hyperenhancement, capsule appearance, washout appearance, and threshold growth.

- The use of liver directed therapy as a bridge to transplant and in downstaging patients is common practice.

- HCC patients must wait 6 months from listing before being granted a MELD exception score of 28, and the MELD score then increases via extension every 3 months to a maximum score of 34.

- Liver transplantation to treat HCC within the Milan criteria has good outcomes with a 5-year disease-free survival rate comparable to patients transplanted without malignancy.
HCC Treatment
Liver Transplantation for Small HCC: Milan Criteria

- 48 patients with cirrhosis and HCC
  - Single tumors ≤ 5 cm or no more than 3 nodules, ≤ 3 cm
  - No vascular invasion
  - No distant metastases
- 75% 4-year survival, 83% recurrence-free
- 27% exceeded criteria on path review
- 50% 4-year survival, 59% recurrence-free

HCC Treatment
Liver Transplantation for Small HCC: Milan Criteria

HCC Treatment
UNOS Criteria for Liver Transplantation for HCC

- Liver ultrasound
- CT or MRI of abdomen showing tumor(s)
  - One 2-5 cm or two or three nodules all < 3 cm
- CT of chest that rules out metastatic disease
- One of the following:
  - a vascular blush in the lesion
  - an alpha-fetoprotein level of >200 ng/ml,
  - an arteriogram confirming a tumor
  - biopsy confirming HCC
  - chemoembolization, RFA, cryo, or chemical ablation
- Rising AFP ≥ 500 ng/ml if no evidence of a mass
HCC Treatment Survival After Transplant for HCC: UNOS Experience

Cumulative Survival

Days

P<0.001

Patients at Risk

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>1 Year</th>
<th>2 Year</th>
<th>3 Year</th>
<th>4 Year</th>
<th>5 Year</th>
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<tr>
<td>1987-1992</td>
<td>433</td>
<td>141</td>
<td>105</td>
<td>80</td>
<td>62</td>
<td>51</td>
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<tr>
<td>1996-2001</td>
<td>270</td>
<td>227</td>
<td>141</td>
<td>70</td>
<td>29</td>
<td>9</td>
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</tbody>
</table>

HCC Treatment
Survival of UNOS Patients Given Extra MELD Points (710 of 904 had HCC)

Cumulative Survival Rate (%)

Days of Patient Survival

1 - Pre-MELD (n = 14,593)
2 - Actual MELD (n = 2,038)
3 - Extra-MELD (n = 904)

P = 0.7

HCC Treatment
Long-Term Survival After OLT for HCC: Humboldt University, Berlin

Pre OLT selection criteria:
- Up to 5 cm
- Up to 3 nodules (≤ 3 cm)

Survival (%)

No HCC (n=940)
HCC (n=120)

Years

HCC Treatment
Expanding the Criteria for Liver Transplantation:
UCSF Criteria 2001

Meet New Staging Criteria

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<th>Yes</th>
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<td></td>
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<td>3725</td>
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<tr>
<td>No</td>
<td>105</td>
<td>42</td>
<td>10</td>
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</table>

Predictors for poor survival:
• AFP >1000, total tumor > 8 cm, age > 55, poorly differentiated histology
Study drawbacks: Retrospective; size based on explant pathology, not on pre-listing or pre-transplant radiology
By “Intention-to-Treat analysis”, survival is comparable between OLT and Resection

Drop-out rate and waiting time are key

• 77 surgical resection
  — 1-, 3- and 5-year survival: 85%, 62%, 51%

• 87 listed for OLT with known HCC

• 8 patients dropped-out due to tumor progression (6) and liver failure (2)
  — 1-, 3- and 5-year “Intention-to-Treat” survival: 84%, 69%, 69%

HCC Treatment
Resection versus Transplantation

**RESECTION**
- Potentially curative
- Readily available
- Non-cirrhotic or...
- Compensated cirrhosis without significant portal hypertension
- Higher rate of recurrence of HCC
- Better survival within 3 years
- No immunosuppression
- Lifetime surveillance

**TRANSPLANTATION**
- Potentially curative
- Advanced cirrhosis
- Shortage of donor livers
- Drop-out while awaiting transplantation
- Higher post-operative mortality; significant morbidity from recurrent hepatitis C no longer an issue
- Lifetime immunosuppression
## HCC Treatment
Resection vs. Transplant for HCC
Three Year Recurrence Rates

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Number</th>
<th>Recurrence</th>
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<tr>
<td></td>
<td>Resection</td>
<td>Transplant</td>
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<tr>
<td>Iwatsuki 1991</td>
<td>76</td>
<td>105</td>
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<tr>
<td>Michel 1995</td>
<td>20</td>
<td>21</td>
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<tr>
<td>Vargas 1995</td>
<td>35</td>
<td>11</td>
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<tr>
<td>Tan 1995</td>
<td>12</td>
<td>15</td>
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<tr>
<td>Otto 1998</td>
<td>52</td>
<td>50</td>
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<tr>
<td>Llovet 1999</td>
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<td>87</td>
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<tr>
<td>Weimann 1999</td>
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<td>31</td>
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<tr>
<td>Figueras 2000</td>
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<td>85</td>
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<tr>
<td>DeCarlis 2001</td>
<td>154</td>
<td>121</td>
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<tr>
<td><strong>Overall</strong></td>
<td><strong>20.0-70.0%</strong></td>
<td><strong>0-43.0%</strong></td>
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# HCC Treatment
**Survival After Resection vs. Transplant**

<table>
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<th>Author/Year</th>
<th>Number</th>
<th>3-Year Survival</th>
<th>5-Year Survival</th>
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<tr>
<td></td>
<td>Resection</td>
<td>Transplant</td>
<td>Resection (%)</td>
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<tr>
<td>Ringe 1991</td>
<td>131</td>
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Recurrence-Free Survival by Radiographic Size Criteria

Within Milan

Downstaged to Milan

Outside Milan, no downstage

P < 0.001
Recurrence-Free Survival by Vascular Invasion

Surgical Management of HCC
Conclusions: Transplant for HCC

- Best option for selected patients with early HCC and little or no fibrosis
- Most HCC in USA is not resectable
- Evaluation and listing for transplant is complex and burdensome, but potentially lifesaving
- All members of the multi-disciplinary team play a role and have a say in the outcome
Thank you!