Management of Liver Cancer: In the Era of Liver Transplantation

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I have no financial conflict of interest to disclose and will not discuss off-label use of products
Hepatocellular Cancer (HCC)

- Highly prevalent disease worldwide with late presentation in most patients
- Rising incidence due to aging population of Hepatitis C patients in the U.S.: 2-5%/yr with cirrhosis
- Targeted therapy of viral hepatitis likely reduces risk of HCC
- Regular surveillance of at-risk patients may offer additional therapies and improve outcomes
Surgical Treatment

- Usually limited to segmental resection
- Limited by cirrhosis and disease burden
- Limited by expertise
- Does not address cirrhosis and new HCC
Hepatocellular Carcinoma

Resection: Cirrhosis vs. No Cirrhosis

![Graph showing survival rates for Hepatocellular Carcinoma resection with and without cirrhosis. The graph indicates a lower survival rate for patients with cirrhosis compared to those without cirrhosis over a period of 7 years.]
Hepatocellular Carcinoma

Resection: Sectorectomy
Cirrhosis
Hepatitis C
Vascular invasion

%<br>0 6 12 18 24 30 36 42 48 54 60 months

early recurrence — late recurrence

p<0.05
## Hepatocellular Carcinoma

### Percutaneous Ethanol Injection

#### Survival Rates (%)

<table>
<thead>
<tr>
<th>Child class</th>
<th>1-yr</th>
<th>3-yr</th>
<th>5-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>96</td>
<td>72</td>
<td>51</td>
</tr>
<tr>
<td>B</td>
<td>90</td>
<td>72</td>
<td>48</td>
</tr>
<tr>
<td>C</td>
<td>94</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

* < 3cm, 93/112 single

Hepatocellular Carcinoma

Recurrence After Ablation

Ultrasound Guided RFA

Recurrence After RFA

New site

Treated site

R Lencioni et al., Radiology 2005;234:961
Hepatocellular Carcinoma

Residual Tumor After Ablation

• NCI, Milan
• 50 pts cirrhosis and HCC, 60 nodules
  ➢ RFA followed by OLT, median time 9.5 months
• 45% have tumor residual
• Risk factors:
  ➢ Tumor size > 3cm

Hepatocellular Carcinoma

Residual Tumor After Ablation

Henry Ford Hospital

- 17 pts: HCC, RFA followed by transplant
- 65% with 100% histologic necrosis
- 82% with > 70% histologic necrosis
- Significance of 100% necrosis
- Role for dual therapy
Hepatocellular Carcinoma

Dual Therapy: RFA +/- TACE

Dual therapy

Hepatocellular Carcinoma

Resection vs RFA

- 148 pts, single, small (≤ 4cm)
- RFA: 55 pts, Resection: 93 pts
- Recurrence:
  - RFA: 58.2%---- 40% remote, 18.2% local
  - Resection: 45.2%---- 43% remote, 2.2% local
- Survival:
  - RFA: 100%, 72.7% at 1 & 3 yrs
  - Resection: 97.9%, 83.9% at 1 & 3 yrs

Hepatocellular Carcinoma

RFA FOR HCC: WHERE DO WE STAND?

“…RFA, differently from resective surgery, does work as a tumor-debulking procedure whose effectiveness decreases over time…”

V. Mazzaferro 2004
Liver Transplantation for Hepatocellular Carcinoma

Rationale: CIRRHOSIS

- High rate of intra-hepatic recurrence
- Removal of the carcinogenic focus
- Significant rate of lesional recurrence
- Higher probability of surgical cure in early cases
- Liver failure in cirrhotic patients
# Liver Transplantation for Hepatocellular Carcinoma

## Early Results

<table>
<thead>
<tr>
<th>Center</th>
<th>Survival (%)</th>
<th>Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 yr</td>
<td>2 yr</td>
</tr>
<tr>
<td>Cincinnati</td>
<td>45</td>
<td>30</td>
</tr>
<tr>
<td>UCLA</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>Cambridge</td>
<td>45</td>
<td>38</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>64</td>
<td>47</td>
</tr>
</tbody>
</table>
Liver Transplantation for Hepatocellular Carcinoma

Importance of Patient Selection

• National Cancer Institute, Milan
• 48 patients with HCC underwent OLT:
  – Single lesion, tumor ≤ 5 cm,
  – < 3 lesions, none > 3 cm
• Survival: 75% at 4 years

Liver Transplantation for Hepatocellular Carcinoma

MELD Exception for HCC

• Delay in reaching transplantation
• Transition to Model of End-stage Liver Disease (MELD)
• HCC gets MELD exception:
  – T2 disease (within Milan)
  – 15% mortality risk at 3 months, upgraded 10% every 3 months
## Liver Transplantation for Hepatocellular Carcinoma

### Prognostic Factors Affecting Survival

#### 10-year survival: multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>CI (95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall patient survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milan criteria (in vs. out)</td>
<td>3.1</td>
<td>1.35-6.93</td>
<td>.007</td>
</tr>
<tr>
<td><strong>Tumor-free survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milan criteria (in vs. out)</td>
<td>5.5</td>
<td>1.39-21.27</td>
<td>.01</td>
</tr>
<tr>
<td>Microsatellites (yes vs. no)</td>
<td>3.6</td>
<td>1.5-8.71</td>
<td>.004</td>
</tr>
<tr>
<td>Microvascular invasion (yes vs. no)</td>
<td>3.4</td>
<td>1.36-8.76</td>
<td>.009</td>
</tr>
<tr>
<td>Tumor grade (G3 vs. G1-2)</td>
<td>3.4</td>
<td>1.04-11.14</td>
<td>.04</td>
</tr>
</tbody>
</table>

Liver Transplantation for Hepatocellular Carcinoma

Tumor Management Prior to Transplant

• Maintain tumor selection criteria

• Monitor progression with serial imaging

• Waiting time challenges:
  – Treat the tumor to halt progression
  – Reduce drop out rate

• Fast track: Living donor, extended criteria donors
Pre-Transplant Tumor Embolization
Liver Transplantation for Hepatocellular Carcinoma

Pre-Transplant Tumor Ablation

• Minimize drop off from list 2ry to disease progression
• ? Better outcomes after liver transplant
• Downstage those beyond Milan to within Milan
• Selection bias
• Waiting time
• No randomized studies
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Pre-Transplant Tumor Ablation

- Henry Ford Hospital
- 2000-2008. OLT for HCC, Milan criteria
- 145 OLTs:
  - 8% exceeded size by Milan (pre), 14% (path)
- 13% (19pts) recurred within 3 years
  - Majority extrahepatic (lung)
- Risk factors worse survival: Additive tumor volume (explant), vascular invasion, poor differentiation
- Lower recurrence with Pre-OLT tumor therapy
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UCSF Modified Staging:

- Cohort 70 patients
- Solitary tumor < 6.5 cm
- < 3 nodules:
  - Largest < 4.5 cm
  - Total diameter < 8 cm
- 60 patients met criteria
- Difference in survival: p = .0029
- Waiting time

F Yao et al., *Hepatology* 2001;33(6):1394
Liver Transplantation for Hepatocellular Carcinoma

Patterns of Recurrence

- Henry Ford Hospital
- HCC: 70 pts 1996-2005
- Recurrences:
  - 13 recurrences (18%)
    - 10 in < 1 yr, all viral etiology
    - 10 were distant recurrences
  - Median survival: 9 months
- AFP has low sensitivity
HCC Recurrence After Transplant

Therapeutic Challenges

- Resect, sirolimus, sorafenib
- Radiosurgery, sirolimus monotherapy
- Free of disease

OLT 1 year 2 year 3 year

Graph showing recurrence and treatment options post-OLT.
Liver Transplantation for Hepatocellular Carcinoma

Managing Recurrence After Transplant

- Reduce immunosuppression
- Directed tumor therapy:
  - Resection, limited disease burden
  - Ablation: Radiosurgery, Radiofrequency, TACE
- Sirolimus (Rapamycin): mTOR inhibition, anti-proliferative
- Sorafenib (Nexavar): MultiKinase inhibitor (proliferation, angiogenesis)
- Shorter follow-up intervals and imaging
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Beyond Milan: Metroticket Calculation

• Web-based survey, NCI (Milan)
  – www.hcc-olt-metroticket.org
• Tumor criteria: Size, number, microvascular invasion
• Expand Milan criteria; Predictive survival model
• 1556 OLT for HCC: 1112 within and 444 outside Milan criteria based on explant
• 41% microvascular invasion: Doubled HR of death
• 283 pts, no invasion:
  – “Up-to-Seven”: largest size (cm) + number of lesions
  – 5 yr overall survival 71.2%
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Beyond Milan: Milan vs. “Up-to-Seven”

V Mazzaferro et al., *Lancet Oncology* 2009;10:35
Liver Transplantation for Hepatocellular Carcinoma

http://www.hcc-olt-metroticket.org
Liver Transplantation for Hepatocellular Carcinoma

5-yr predicted survival: 59.5%

95% confidence interval: 56.9 - 62.1%
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Vascular Invasion Absent: 68.4%

95% confidence interval: 64.1 - 72.2%
Liver Transplantation for Hepatocellular Carcinoma

Vascular Invasion Present: 46.3%

95% confidence interval: 40.6 - 51.9%
Indications of partial hepatectomy for transplantable hepatocellular carcinoma with compensated cirrhosis
Resection for Hepatocellular Carcinoma

Risk Factors

- Histologic surgical margin (≤5 mm)
- Child-Pugh grade (B)
- Hepatitis virus (C)

0-1 factor

2-3 factors
Resection for Hepatocellular Carcinoma

Disease Free Survival

Weitz, Ann Surg 2011
Hepatocellular Carcinoma

Multi-modality Therapy in Evolution

Modified from K. Okuda, National Cancer Center Hospital, Tokyo
Hepatocellular Carcinoma

Standard of Care Dictates Referral of Stage I and II HCC Patients with Cirrhosis for Transplant Evaluation
Liver Transplantation for Hepatocellular Carcinoma

Summary

• Liver transplant has improved outcome for HCC
• Patient selection using Milan yields superior outcomes
• Beyond Milan: Tumor biology (vascular invasion, grade) and accurate staging with enhanced imaging are critical
  – Metroticket calculation
• Modulating immunosuppression: CNI $\rightarrow$ Sirolimus, probably helpful but should be studied
• Recurrence: Modulate immunosuppression, Sorafenib, directed therapy selectively
NCAA Championship

Final | 1 | 2 | T
--- | --- | --- | ---
#2 Kansas | 27 | 32 | 59
#1 Kentucky | 41 | 26 | 67

The Courier-Journal

RETURN TO GLORY

WILDCATS BEAT KANSAS FOR 8TH NCAA TITLE